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The Effect of Aureomycin and Chloramphenicol on the Fungal and Bacterial Flora of Children 397
Joseph J. McGovern, Robert H. Parrott, Chester W. Emmons, Sidney Ross, Frederic G. Burke and E. Clarence Rice

Management of Bleeding from the Upper Gastrointestinal Tract 404
Stanley O. Hoerr

The Precipitin Test for Bence-Jones Protein . 409
Fred C. Collier and Paul Jackson

Medical Progress: Pharmacologic Aspects of Adrenocortical Steroids and ACTH in Man 414
(To be continued)
George W. Thorn et al.

Massachusetts Medical Society 438
Massachusetts Department of Public Health . 438
Correspondence 439

Medical Intelligence:

The Identification of Pentobarbital by Paper Chromatography in a Medicolegal Death 423
Elvera J. Algeri and Arthur J. McBay

Doctors Afield: Samuel Gridley Howe . . 424
Peter Pineo Chase

Case Records of the Massachusetts General Hospital 426

Editorials:

The Doctor Takes His Pen in Hand 436
To the Absent Members 437
Appraisal of the Adolescent 437

Book Review 439
Books Received 439
Notices 440

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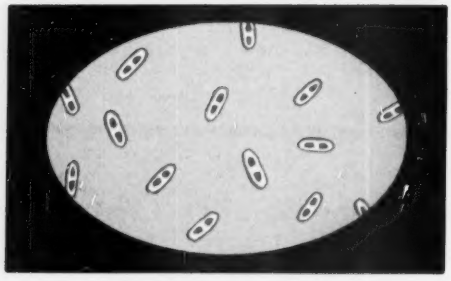

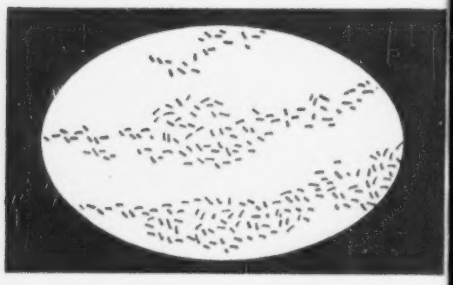

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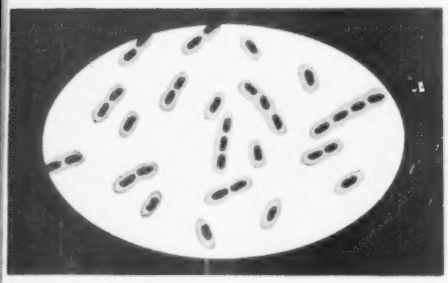

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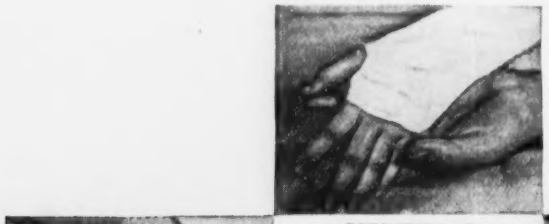

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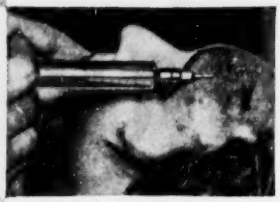

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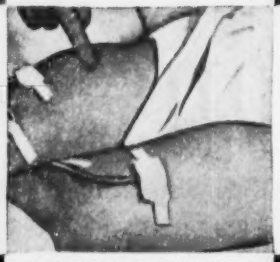

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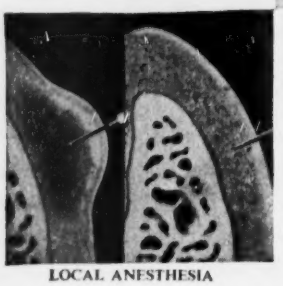

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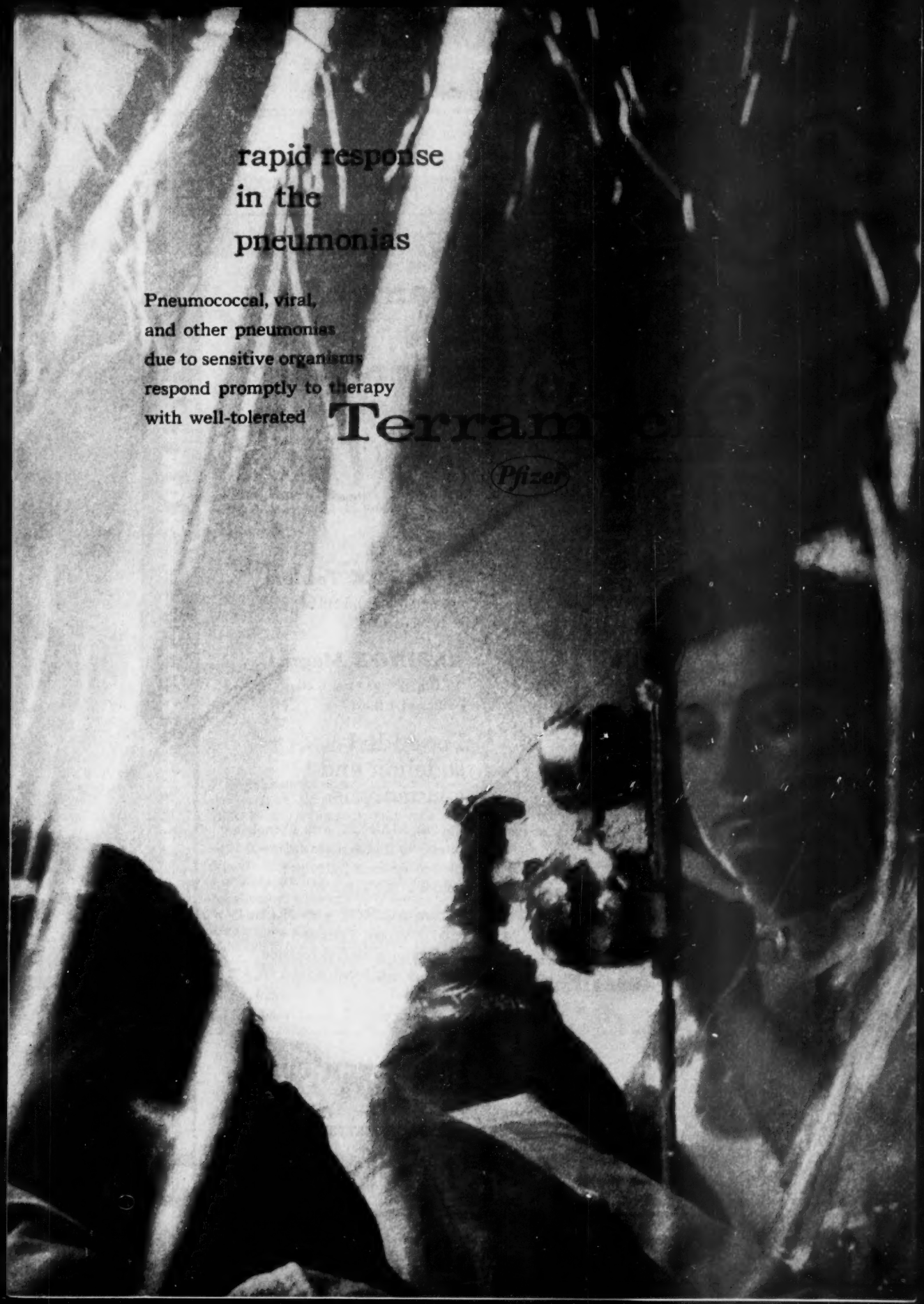
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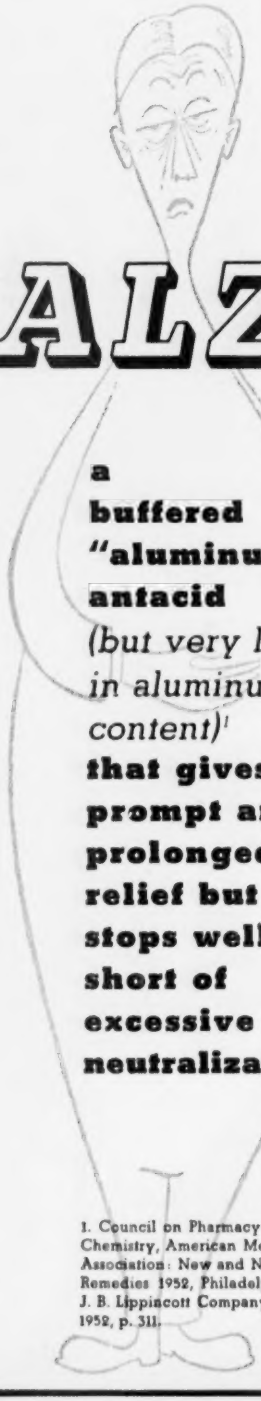

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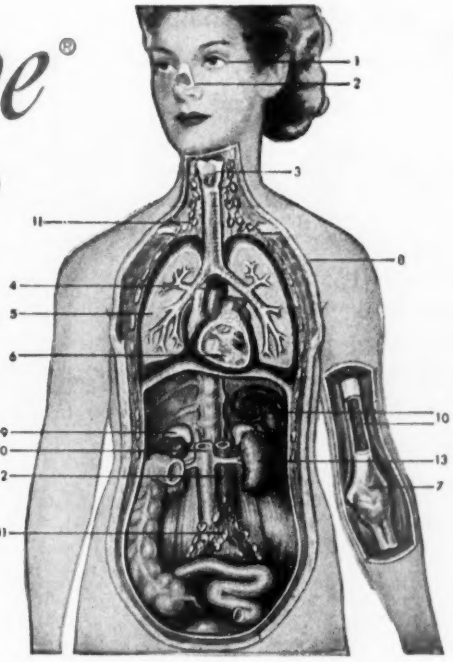

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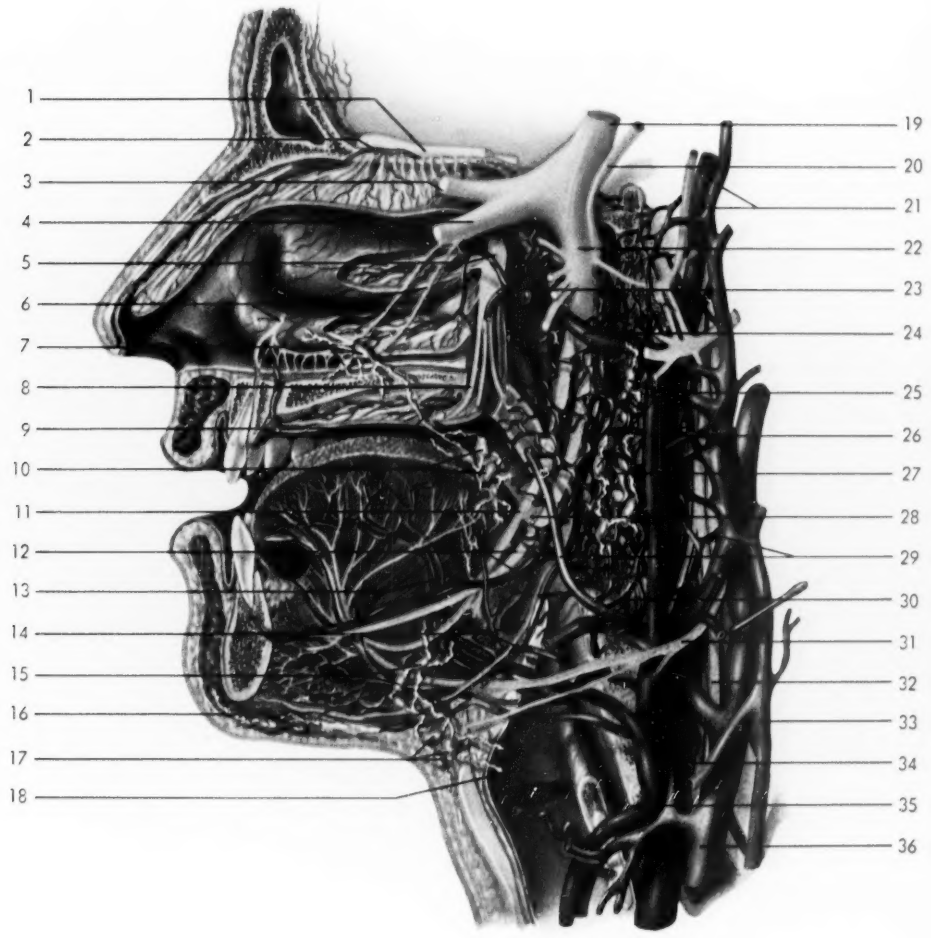

1. Olfactory nerve
2. Anterior ethmoidal artery
3. Ophthalmic nerve
4. Maxillary nerve
5. Sphenopalatine ganglion
6. Anterior, middle & posterior superior alveolar nerves
7. Maxillary lymph nodes
8. Anterior palatine nerve
9. Great palatine artery
10. Buccinator lymph nodes
11. Lingual nerve
12. Inferior alveolar nerve & artery
13. Lingual artery & vein
14. Mylohyoid nerve & artery
15. Supramandibular lymph nodes
16. Submental lymph nodes
17. Submaxillary lymph nodes
18. Trachea
19. Sensory root of trigeminal nerve
20. Motor root of trigeminal nerve
21. Superficial temporal artery & vein
22. Mandibular nerve
23. Sphenopalatine artery
24. Internal maxillary artery
25. Parotid lymph nodes
26. External carotid artery
27. Pterygoid venous plexus
28. Oropharynx
29. Anterior & posterior facial veins
30. External maxillary artery
31. Hypoglossal nerve
32. Vagus nerve
33. External jugular vein
34. Internal carotid artery
35. Esophagus
36. Internal jugular vein

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Volume 248 MARCH 5, 1953 Number 10

THE EFFECT OF AUREOMYCIN AND CHLORAMPHENICOL ON THE FUNGAL AND BACTERIAL FLORA OF CHILDREN*

JOSEPH J. McGOVERN, M.D.,† ROBERT H. PARROTT, M.D.,‡ CHESTER W. EMMONS, Ph.D.,§ SIDNEY ROSS, M.D.,¶ FREDERIC G. BURKE, M.D.,|| AND E. CLARENCE RICE, M.D.**

WASHINGTON, D. C.

SEVERAL reports in the literature have suggested that chloramphenicol and aureomycin commonly have undesirable side effects, especially involving the mucous membranes.[1-3] These include glossitis, stomatitis, sore throat, proctitis, pruritus vulvae and ani, nausea, vomiting, diarrhea, bronchomoniliasis, mycotic endocarditis and meningitis, and the sprue syndrome.[4-8] Oral manifestations alone have been recorded in 6 to 20 per cent of patients who received aureomycin or chloramphenicol.[1] Nearly all the patients in whom these complications occurred have been adults who had received relatively long-term therapy.

The explanations for these phenomena vary. One hypothesis advanced suggests that they are a direct result of increased growth of *Candida albicans*.[9, 10] Another theory proposes that these reactions represent evidence of vitamin B deficiency, which in turn may permit the development of moniliasis. However, there is little definitive laboratory evidence to support either view.[11, 12]

Among the species of candida that can be isolated from the respiratory and gastrointestinal tracts, only *C. albicans* is commonly recognized as an important pathogen. However, *C. parakrusei* and *C. guillermondi* have been isolated from the lesions of endocarditis in drug addicts; *C. krusei* has been associated with an unusual tonsillar infection and with certain outbreaks of infant diarrhea, and *C. tropicalis*, which is frequently present in the gastrointestinal and respiratory tracts without causing disease, may have potential pathogenicity.[13] Experimentally, bronchomoniliasis has been produced in guinea pigs by the insufflation of *C. tropicalis* into the tracheobronchial tree.[14] The object of the present investigation has been, first, to determine the incidence of *C. albicans* in the gastrointestinal tract of normal children of various ages and, secondly, to observe and correlate the clinical, bacteriologic and mycologic alterations that occur in children after the short-term administration of broad-spectrum antibiotics.

METHOD AND MATERIALS

The first phase of the experiment dealt with the incidence of *C. albicans* in the mouths and rectums of 100 normal children from one month to twelve years of age. The children selected were free of detectable infectious disease and had not received antibiotics in recent weeks. Approximately 70 per cent of this group of subjects were from the well-baby clinic and wards of the Children's Hospital, Washington, D. C., and the remaining 30 per cent were from an institution for convalescent children in the environs of Washington, D. C.

In the second phase of the experiment therapeutic doses of two broad-spectrum antibiotics were given to selected groups of children.

Aureomycin

Aureomycin was given orally for eight days to 21 hospitalized children in whom there was no medical indication for antibiotic therapy. The ages of these children ranged from five months to ten years. There were 12 boys and 9 girls (13 white and 8 Negro patients). The dosage was 40 to 50 mg. per kilogram of body weight in divided doses over a twenty-four-hour period, the average total dose being 8 gm. None of the children had acute infections or diseases involving the oral mucous membrane, nor had they received antibiotic therapy within recent weeks. Since many of the children were not old enough to swallow a 250-mg. capsule

*From the Research Foundation of Children's Hospital, and the Microbiological Institute, National Institutes of Health, Public Health Service, Federal Security Agency.

The medications employed in this study were kindly supplied by Parke, Davis and Company, Detroit, and by the Lederle Laboratories, New York City.

†Junior assistant resident in pediatrics, Children's Medical Center, Boston; formerly, intern in pediatrics and fellow of Research Foundation, Children's Hospital, Washington, D. C.

‡Instructor in clinical pediatrics, Georgetown University School of Medicine; junior associate attending physician, Children's Hospital; senior assistant surgeon, United States Public Health Service.

§Professorial lecturer, George Washington University School of Medicine; mycologist, National Microbiological Institute, National Institutes of Health, United States Public Health Service.

¶Assistant clinical professor of pediatrics, Georgetown University School of Medicine; associate attending physician, Children's Hospital.

||Professor of pediatrics, Georgetown University School of Medicine; chief of pediatrics, Georgetown University Hospital; associate attending physician, Children's Hospital.

**Associate professor of pediatrics (pathology), Georgetown University School of Medicine; director of laboratories, Garfield Memorial and Children's hospitals.

of aureomycin, the powder was removed from the capsule and mixed with milk or chocolate syrup in all cases to ensure uniformity of administration.

Bacteriologic and mycologic studies from the mouth and rectum of each patient were made on three consecutive days before treatment. During the eight-day period of aureomycin administration, mouth and rectal specimens were obtained for bacterial and fungal study on the first three days and on alternate days thereafter until the aureomycin was discontinued. After this time specimens were again collected for three consecutive days and on alternate days thereafter for a second eight-day period. During the entire period of study the average number of cultures made on each patient, for bacteria and fungi, was 13 each from the mouth and rectum.

Chloromycetin (Chloramphenicol) Palmitate

Chloramphenicol was given to 15 children who had no acute infectious disease at the Children's Convalescent Home, an institution for recuperating children in the suburbs of Washington, D. C. There were 5 female and 10 male patients ranging in age from five months to three years and consisting of 8 white and 7 Negro children. They were given Chloromycetin (chloramphenicol) Palmitate by mouth, 100 mg. per kilogram of body weight in divided doses over a twenty-four-hour period. Therapy was continued for fourteen days. The average total dose was 16 gm.

A group of 10 children of comparable age, sex and racial distribution, all living in the same environment, was selected as a control. Both groups received adequate amounts of a synthetic multivitamin preparation, including the vitamin B complex, daily. Material from the mouth, rectum and vagina of both control and treated groups was obtained by the swab method for mycologic examination only on two consecutive days prior to treatment and on alternate days during and after the treatment for a total study time of a month. Mycologic examinations of each site were carried out on each patient on the average of sixteen times.

Intramuscularly Injected Chloramphenicol

In a third study serial bacterial and fungus studies were carried out on an additional 9 children who had been hospitalized for infectious croup and treated with intramuscular injections of chloramphenicol. The average duration of hospital stay was twelve days. These patients received the antibiotic by the intramuscular route in a dosage of 100 mg. per kilogram of body weight per twenty-four hours for an average of eight to ten days. They also were given a multiple vitamin preparation daily. The average number of cultures for bacteria and fungi examined on each patient was six, the material for only one of which was obtained before the start of therapy.

For the studies of oral fungi a dry sterile swab was rubbed over the gingivas, tongue and buccal mucosa and then streaked across two Sabouraud-agar slants. For the rectal-fungus studies, a dry swab was inserted a distance of 5 cm. into the anus, and the specimen of the stool thus obtained was streaked on two Sabouraud-agar slants. We obtained vaginal material by touching a dry sterile swab to the mucosa and streaking the swab on two Sabouraud-agar slants.

The total numbers of colonies of yeast-like fungi on both slants were counted, and an average obtained. By this method some measure of quantitative change in serial cultures from the same patient was obtained. The designation "few" was used when there were less than 10 colonies, "moderate", when there were between 10 and 20 colonies, "many" when there were between 20 and 50 and "very many" when between 50 and 100 colonies or confluent growth developed.

In identifying the strains of yeast-like fungi isolated from these patients the cultures were purified when necessary by subculturing on Sabouraud's agar to which penicillin and streptomycin were added at levels approximating 20 units of each per cubic centimeter of agar. They were then subcultured on cornmeal agar to determine whether hyphae were produced and to identify *C. albicans*. This abbreviated procedure was sufficient to identify most strains of *C. albicans*. If there was doubt about the identity of *C. albicans* or if another species was involved strains were subcultured twice on sugar-free meat-extract agar and then transferred to sugar broths, the procedures outlined by Martin et al.[15] being followed. Yeasts were identified as such by the absence of hyphae on cornmeal agar and, in most cases, by the formation of ascospores on either cornmeal or meat-extract agar.

The same sampling methods were used to obtain specimens from the mouth and rectum for bacteriologic studies when they were done concomitantly with the fungus studies. Mouth cultures were incubated overnight at 37°C. in exactly 2.5 cc. of Difco brain-heart infusion broth. From this culture a single 2-mm. inoculating loopful was streaked on half of a Difco-base blood-agar plate. The resulting growth was examined for various bacterial organisms. An approximately quantitative classification was made and the number of colonies present were described as "few," "moderate" or "many." Stool cultures were done on each patient, the swab technic being employed. Difco S. S. agar plates were streaked and incubated overnight at 37°C. Organisms were identified according to their colonial morphology on selective mediums. Organisms that could not be identified on selective mediums were identified by their biochemical activity. Quantitative descriptions of stool cultures were made in the same manner as for the throat cultures. (Throughout this paper the term "quantitative" is used to

designate only a comparison of the approximate numbers of colonies isolated by the technics used.)

Frequent clinical examination was made of the oral cavity, vagina and rectum of each child who received antibiotic therapy, as well as of the children used as controls. Observations of complications and side effects such as vomiting, diarrhea and nausea were made daily and recorded. To ensure uniformity of technic all the collection of specimens and clinical observations were made or directly supervised by two of us. The fungus studies were all performed by one of us. The bacteriologic studies were conducted by the staff of the Antibiotic Laboratory of the Research Foundation of Children's Hospital, Washington, D. C.

Incidence of *C. albicans* in the Gastrointestinal Tracts of Normal Children

C. albicans has been found in 6 to 24 per cent of the mouths of normal adults in different surveys.[16-18] Lilienthal[19] demonstrated that the incidence was 10 per cent higher when saliva, accumulated over a period of five minutes, was examined rather than the material obtained from a single swab from the mouth. In the only report found dealing with children, *C. albicans* was encountered in 5 per cent of 35 children examined by the swab method. These children were selected at random from a hospital population, and the ages were not given. Schnoor,[20] studying medical students and hospitalized patients at Duke University, found that 16 per cent of normal stools contained *C. albicans* in small quantities, but that only 1 per cent had 12 or more colonies appearing on the surface of the agar.

Table 1. *Incidence of* C. Albicans *in the Mouths and Rectums of 100 Normal Children, According to Age.*

Age	Mouth			Rectum		
	No. tested	No. positive	Per-centage	No. tested	No. positive	Per-centage
1-11 mo.	28	3	10.7	14	1	7.1
12-23 mo.	26	4	15.1	13	1	7.6
2-5 yr.	23	2	8.7	18	0	—
6-12 yr.	23	5	21.7	23	2	8.7
Totals	100	14		68	4	
Averages			14.0			6.0

In the present series of fungus cultures from 100 normal children, the incidence of *C. albicans* was 14 per cent in the mouth and 6 per cent in the stool. The average number of colonies that appeared on the surface of an agar slant was 3. There was no significant difference in the occurrence of *C. albicans* within the groups from the Well Baby Clinic, the hospital or the convalescent home. The incidence, analyzed according to age, is found in Table 1, which shows that there is little difference among these arbitrarily selected age groups.

Effect of Aureomycin on Bacterial and Fungal Flora of Gastrointestinal Tracts of Children

Strictly speaking, broad-spectrum antibiotics do not render the gastrointestinal tract "sterile." Instead, they temporarily suppress the growth of certain groups of organisms while permitting the overgrowth of other, more resistant bacteria and fungi. In a detailed bacteriologic study, Meads[21] described the changes in the bacterial flora of the throat that take place during oral treatment with aureomycin, pointing out the incidental finding of *C. albicans* in 20 per cent of his patients during therapy.

In our study an attempt was made to observe specifically the quantitative changes in bacterial and fungal flora, with particular reference to *C. albicans*, which occurred in 21 hospitalized children who were given aureomycin by mouth for eight days. From the cultures obtained before therapy it was observed that in the mouth *Neisseria catarrhalis* was the organism found most commonly and in the greatest numbers, *Micrococcus pyogenes* (var. *albus*), alpha-hemolytic streptococcus, *Diplococcus pneumoniae* and beta-hemolytic streptococcus being found less frequently, and in fewer numbers, in that order. Tables 2 and 3 illustrate the bacteriologic

Table 2. *Positive Cultures for Various Bacteria and Candida from the Mouths of 21 Children before, during and after Treatment with Aureomycin.**

	Before Treatment		Third Day of Treatment	Eighth Day of Treatment	Third Day after Treatment	Eighth Day after Treatment
	No.	Per-centage	Per-centage	Per-centage	Per-centage	Per-centage
C. albicans:						
Many	10		25	25	20	10
Moderate	5		0	0	5	5
Few	10		0	5	0	10
None	75		75	70	75	75
Other candida species:						
Many	0		0	0	0	0
Moderate	0		0	0	0	0
Few	0		5	15	5	0
None	100		95	85	95	100
M. pyogenes (var. *albus*):						
Many	10		10	10	10	10
Moderate	30		40	30	20	20
Few	20		10	20	30	30
None	40		50	40	40	40
N. catarrhalis:						
Many	60		20	0	30	60
Moderate	20		10	20	20	20
Few	20		30	20	20	20
None	0		40	60	30	0
Alpha-hemolytic streptococcus:						
Many	30		10	0	10	30
Moderate	10		10	20	10	10
Few	20		30	20	30	20
None	40		50	60	50	40
Beta-hemolytic streptococcus:						
Many	0		0	0	0	0
Moderate	0		0	0	0	0
Few	20		0	0	10	20
None	80		100	100	90	80
Pneumococcus:						
Many	0		0	0	0	0
Moderate	0		0	0	0	0
Few	50		10	0	20	50
None	50		90	100	80	50

*Calculated within 5 per cent.

and mycologic flora of the mouths and rectums of these children, as demonstrated by the selective technics used, as well as changes that had taken place at the third and the eighth day after treatment had been discontinued. *C. albicans* was found in small numbers (2 or 3 colonies per slant) in the mouths of 25 per cent of the children before aureomycin therapy. None of the other species of candida were found in the patients before treatment.

In the rectum *Esch. coli* was the bacterial organism found most commonly and in the largest numbers, whereas *P. vulgaris* and *Ps. aeruginosa* were also present but in smaller numbers. *C. albicans* was found in the rectum in small numbers (2 or 3 colonies) in 15 per cent of the patients before aureomycin was begun. No other species of candida were found in the rectum before treatment.

During the eight-day period of treatment the changes that took place in the bacterial flora of the mouth coincided with those observed in other published reports.[21] Alpha-hemolytic and beta-hemolytic streptococcus, *D. pneumoniae* and *N. catarrhalis* were regularly reduced in number within seventy-two hours and were largely absent at the end of eight days of treatment with aureomycin. The effect on *M. pyogenes* (var. *albus*) was less striking and not at all predictable. After withdrawal of the drug, the normal bacteriologic flora quickly became re-established.

C. albicans was somewhat more common in the mouths of the patients after they had received aureomycin for eight days, the incidence rising from 25 per cent before treatment to 30 per cent. There was also a great increase in the number of organisms present before treatment — from an average of 3 to 5 colonies before treatment to 50 to 100 colonies after treatment. Although species of candida other than *C. albicans* were not present before treatment, a few colonies of other species were recovered from 5 per cent of the treated patients by the third day, and many colonies were present in 15 per cent by the eighth day of drug administration. The incidence of *C. albicans* in the rectum was 15 per cent before therapy and 25 per cent after eight days of therapy. As in the mouth, there was a marked increase in the number of colonies isolated from persons in whom organisms had originally been present. No other species of candida was present before treatment, whereas numerous colonies of such organisms were obtained in 20 per cent of the patients after eight days of aureomycin administration. The species of candida other than *C. albicans* recovered from mouth or rectum included *C. tropicalis*, *C. pseudotropicalis* and *C. parakrusei*. At the time the increase in the number of fungi in the rectum appeared, there was an almost simultaneous increase of pseudomonas or proteus organisms. However, this type of bacterial overgrowth was observed with equal frequency in cultures from the patients in whom no fungi were present.

Thus, *C. albicans* was cultured from the gastrointestinal tract (either the mouth or the rectum or both) in 25 per cent of patients before treatment and in 30 per cent after eight days of aureomycin therapy. No species of candida other than *C. albicans* was cultured from the gastrointestinal tract before treatment, whereas after eight days of aureomycin administration such organisms were present in 20 per cent of the cases. The occurrence of these fungi in the mouth and rectum appeared to parallel one another except that in many patients changes in the stool preceded changes in the mouth by twenty-four hours, and in some cases fungi could be demonstrated only in the stool even at the end of the treatment period. In the majority of patients a marked alteration in the fungal flora of the gastrointestinal tract was demonstrable at the end of seventy-two hours of treatment. After discontinuation of aureomycin therapy the length of time necessary for the bacteriologic flora to return to normal was three to five days, whereas it took six to twelve days for the fungal flora to return to normal. The longest time required for restoration of normal fungal flora occurred in patients in whom *C. albicans* had not been found before treatment and had first appeared during therapy with aureomycin. The fungi of the rectum were prone to show more rapid alteration than those of the mouth. In addition, large numbers of yeasts appeared in 15 per cent of the patients during therapy.

TABLE 3. *Positive Cultures for Various Bacteria and Candida from the Rectums of 21 Children before, during and after Treatment with Aureomycin.**

	Before Treatment	Third Day of Treatment	Eighth Day of Treatment	Third Day after Treatment	Eighth Day after Treatment
No.	Per-centage	Per-centage	Per-centage	Per-centage	Per-centage
C. albicans:					
Many	0	10	20	10	0
Moderate	0	10	5	5	0
Few	15	5	0	5	15
None	85	75	75	80	85
Other candida species:					
Many	0	15	15	0	0
Moderate	0	0	5	10	0
Few	0	0	0	0	0
None	100	85	80	90	100
Escherichia coli:					
Many	0	0	0	0	0
Moderate	0	0	0	0	0
Few	50	20	10	40	50
None	50	80	90	60	50
Pseudomonas aeruginosa:					
Many	0	10	20	0	0
Moderate	0	0	0	0	0
Few	10	20	0	0	0
None	90	70	80	100	100
Proteus vulgaris:					
Many	0	0	10	0	0
Moderate	0	20	10	20	0
Few	20	10	10	10	20
None	80	70	70	70	80

*Calculated within 5 per cent.

Clinical Observations in Aureomycin-Treated Group

In the patients on aureomycin treatment, the complications of vomiting, diarrhea and nausea occurred most commonly, in that order, and were adequately managed by the omission of one or two doses of the drug. These manifestations usually appeared within two or three days and once having subsided did not tend to reappear. Although there was a high incidence of *C. albicans* in cultures from the gastrointestinal tract of these patients during the treatment period, there was no clear indication that the presence of the fungus was responsible for these transient signs and symptoms.

Table 4. *Side Effects Observed in 21 Children during Administration of Aureomycin.*

Side Effect	Patients Involved	Average Interval between Onset and Start of Therapy	Average Duration of Side Effect
	%	*days*	*hr.*
Nausea	10	2	24
Vomiting	20	3	24
Diarrhea	15	4	48

Table 4 indicates the incidence, the average interval before appearance and the duration of these complications. There were no lesions observed involving the mucous membranes, nor did clinical thrush develop in any of the patients treated with aureomycin.

Effect of Chloramphenicol on Fungal Flora of Children

Before oral administration of Chloromycetin Palmitate, the fungal floras, in the treated and control groups were essentially the same. During the entire period of study little change was noted in the control group. Among the treated children after fourteen days of chloramphenicol administration, the incidence of *C. albicans* rose from 14 to 28 per cent in the mouth and from 7 to 21 per cent in the rectum. No *C. albicans* colonies were isolated from the vagina.

The incidence of candida species other than *C. albicans* after fourteen days of therapy changed from 7 to 28 per cent in the mouth, from 14 to 42 per cent in the rectum and from 0 to 21 per cent in the vagina. With rare exception, the other types of candida encountered were classified as *C. parakrusei*.

The incidence of geotrichum did not change during antibiotic therapy although there was some increase in the quantity of growth. Yeast forms (saccharomyces), which had not been recovered from any of the group before treatment, were found at the end of treatment in moderate numbers in the rectum in 42 per cent and in the mouth in 14 per cent of the patients who received chloramphenicol.

In children not found to be harboring fungi before therapy *C. albicans* and other species of *candida* appeared for the first time seventy-two hours after treatment had begun. At this time there was also a decided increase in the abundance of growth of these fungi from all patients who had harbored them before treatment. The rate of the increase continued steadily so that by the fourteenth day of treatment the growth of candida on the Sabouraud agar slants was confluent and colonies could not be counted. The return of the fungal flora to its pretreatment state began within three days of the discontinuance of therapy and was complete as a rule by the end of fourteen days.

The changes in the bacterial flora of the mouth which occurred during the intramuscular administration of chloramphenicol to hospitalized patients with croup will be reported in detail elsewhere.[22] The growth of the gram-negative and gram-positive organisms, with the exception of *M. pyogenes* (var. *albus*) and *Ps. aeruginosa*, was diminished within seventy-two hours. A few colonies of *C. albicans* were present in cultures from the mouth in 11 per cent of the members of this group before treatment. By the eighth day of treatment a heavy growth of *C. albicans* could be cultured in 44 per cent.

In summary, of the 24 patients who were treated with chloramphenicol, either orally or intramus-

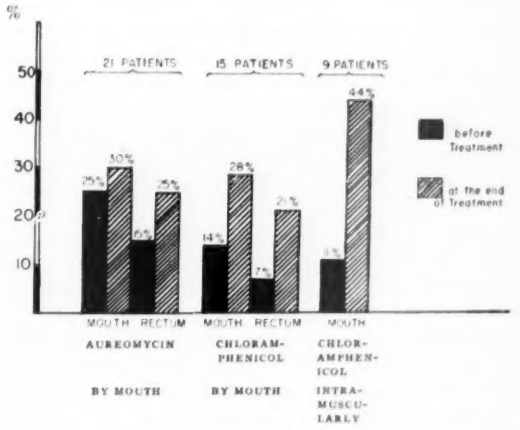

Figure 1. *Comparative Effects of Aureomycin and Chloramphenicol on the Incidence of* C. Albicans.

cularly, *C. albicans* was cultured from the gastrointestinal tract (mouth or rectum or both) in 12 per cent before treatment. After ten to fourteen days of treatment, *C. albicans* was found in the gastrointestinal tract in 32 per cent.

Figure 1 shows the comparative effects of chloramphenicol and aureomycin therapy on *C. albicans* in the gastrointestinal tract.

Clinical Observations in the Chloramphenicol-Treated Group

Within forty-eight hours of the beginning of Chloromycetin Palmitate therapy, frequent loose green stools were noted in 4 patients in the group receiving this drug and in 3 patients in the control group. Symptomatic measures alone were employed in the control group whereas the succeeding one or two doses of the antibiotic were omitted in the treated group. The diarrhea subsided in both groups within thirty-six hours. Cultures for *C. albicans* became positive in the stools at the same time that the diarrhea developed in 1 of the four patients in the treated group. On the other hand, *C. albicans* was not identified in the stools of any of the 3 patients with diarrhea in the control group. This outbreak of diarrhea, then, was in all probability coincidental to the study rather than a result of either the drug or the monilial overgrowth.

No cases of nausea, vomiting, vulvovaginitis, pruritus ani or vulvae, glossitis or thrush developed in the patients treated with chloramphenicol, nor did they refuse their medication. Here again, *C. albicans* appeared in large numbers in cultures from patients at the end of therapy, without the appearance of undesirable side effects or lesions of the mucous membrane.

Discussion

In the present series the incidence of *C. albicans* in the mouths of 100 normal children was 14 per cent, which is approximately the same as that reported in the mouths of adults. The incidence of *C. albicans* in the stools of 68 normal children in this series was 6 per cent, or slightly lower than that reported in adults. There was no significant difference of *C. albicans* found in the gastrointestinal tract of children from the various age groups selected for this investigation.

From the data presented it appears that the effect of the administration of aureomycin and chloramphenicol on the fungal flora of the gastrointestinal tract in children is such that yeast-like fungi, when already present, grow with more abundance. *C. albicans* also becomes demonstrable in a significant number of persons in whom it was not originally found. The reason for this effect is not clear. Several investigators have studied the effect of aureomycin, chloramphenicol, terramycin and penicillin on the growth of *C. albicans* and the results are conflicting. It has been claimed that penicillin stimulates the growth of *C. albicans* in vitro and that it enhances the virulence of this organism for chicks.[23] Other investigators have noted an inhibitory effect on the growth of *C. albicans* by penicillin in vitro. Levi[24] believes that this antibiotic does not alter the virulence of *C. albicans* in vitro for rabbits.

Seligman[25] reports that aureomycin enhances the virulence of *C. albicans* for mice. Lipnik et al.[11] conclude that aureomycin and chloramphenicol do not stimulate the growth of *C. albicans* in vitro and that there is no clear-cut evidence of enhancement of moniliasis in mice receiving various antibiotics. On the other hand, Pappenfort and Schnall[7] report that aureomycin hydrochloride stimulates the growth of *C. albicans* in vitro. Both groups of authors agree that some inert substance, probably a phosphate in the drug capsule itself, may be responsible for the apparent stimulatory effect on the growth of *C. albicans* in vitro. However, in our series the aureomycin powder was removed from the capsules in all cases and mixed in milk or chocolate syrup before being administered to the children. Nevertheless, *C. albicans* appeared in increased numbers in patients after treatment. Thus, it seems clear that the increase of candida in the gastrointestinal tract after administration of aureomycin was not due to the presence of an inert substance in the capsule. This observation may also be extended to the groups in our study treated with chloramphenicol since in no case was this drug given in capsule form.

The changes in the present series in the fungal growth of the gastrointestinal tract that occurred under the influence of aureomycin and chloramphenicol were accompanied by equally noticeable changes in the growth of certain bacteria. Before aureomycin and chloramphenicol therapy approximately 20 per cent of patients showed fungi of some type in the gastrointestinal tract. At the end of the period of treatment fungi or yeasts of some type were present in the gastrointestinal tract in 70 per cent of the entire group studied. This over-all increase in yeast and yeast-like flora coincided in time with a marked decrease in the bacterial flora of the gastrointestinal tract.

Vitamin administration is alleged to be beneficial in the treatment of lesions that develop during the administration of chloramphenicol and aureomycin.[1] In our investigation all the patients who were given chloramphenicol orally or intramuscularly received the commonly recommended multivitamin supplements during the course of the treatment whereas none of those who received aureomycin were given vitamins. Aside from the transient nausea, vomiting and diarrhea noted during aureomycin administration and adequately managed by the omission of one or two doses of the drug, no undesirable side effects resulted from the use of aureomycin or chloramphenicol in therapeutic doses for eight days and fourteen days respectively.

Although *C. albicans* was apparently induced to grow in 17 per cent of the 45 patients observed, clinical thrush did not appear in any patient. However, we have noted clinical thrush in 4 unreported cases in which the broad-spectrum antibiotics were given either in larger doses than those used in this

study or in the same dose for longer periods. It seems that the duration of treatment, the dosage and the presence or absence of *C. albicans* before treatment are important in determining whether thrush or other forms of moniliasis will develop during therapy with broad-spectrum antibiotics. From the results of this study the danger of moniliasis in children from the use of these drugs in therapeutic doses does not seem great when the drug is administered for not more than eight days.

Summary and Conclusions

One hundred normal children were examined to determine the incidence of *Candida albicans* in the gastrointestinal tract. This organism could be demonstrated in small numbers in the mouths of 14 per cent of the children and in the rectum in 6 per cent.

Twenty-one normal children were given aureomycin orally for eight days, and 24 children were given chloramphenicol intramuscularly or orally for ten to fourteen days. Laboratory and clinical observations were made on each child before, during and after the treatment period.

Before treatment the incidence of *C. albicans* in the gastrointestinal tract was 17 per cent in this group of 45 children, rising to 33 per cent at the end of the treatment period. By the third to the eighth day of treatment, the average number of colonies of *C. albicans* had increased from 3 to 50. There was a marked decrease in gram-negative and gram-positive organisms in the gastrointestinal tract, with a concomitant increase in the fungal floras, including yeasts and various species of candida other than *C. albicans*.

We are indebted to Drs. John P. McGovern, Valerie Enright and Marie Kernan who aided in the collection of specimens, to Dr. Donald A. Rowley, who helped in identification of the fungi, and to James Gilroy, M. S., and Rosemary Fiorentino, who aided in the conduction of bacterial studies.

References

1. Tomaszewski, T., and Poznan, M. D. Side-effects of chloramphenicol and aureomycin, with special reference to oral lesions. *Brit. M. J.* **1**:388-392, 1951.
2. Williams, B., Jr. Oral and pharyngeal complications of chloramphenicol (chloromycetin) therapy. *Am. Pract. & Digest Treat.* **1**:897-900, 1950.
3. Ormerod, F. C., and Friedmann, I. Case of moniliasis. *Brit. M. J.* **2**: 1439, 1951.
4. Geiger, A. J., Wenner, H. A., Axilrod, H. D., and Doorlocker, S. H. Mycotic endocarditis and meningitis: report of case due to Monilia albicans. *Yale J. Biol. & Med.* **18**:259-268, 1949.
5. Zimmerman, L. E. Candida and Aspergillus endocarditis with comments on role of antibiotics in dissemination of fungus disease. *Arch. Path.* **50**:591-605, 1951.
6. Merliss, R. R., and Hoffmann, A. Steatorrhea following use of antibiotics. *New Eng. J. Med.* **245**:328-330, 1951.
7. Pappenfort, R. B., and Schnall, E. P. Moniliasis in patients treated with aureomycin. *Arch. Int. Med.* **88**:729-735, 1951.
8. Woods, J. W., Manning, I. H., and Patterson, N. Monilial infections complicating therapeutic use of antibiotics. *J. A. M. A.* **145**: 207-211, 1951.
9. Leitner, Z. A. Vitamin deficiency and antibiotics. *Brit. M. J.* **1**: 491, 1950.
10. Gewin, H. M., and Friou, G. J. Manifestations of vitamin deficiency during aureomycin and chloramphenicol therapy of endocarditis due to Staphylococcus aureus. *Yale J. Biol.* **23**:332-338, 1951.
11. Lipnik, M. J., Kligman, A. M., and Strauss, R. Antibiotics and fungus infections. *J. Invest. Dermat.* **18**:247-261, 1952.
12. Kligman, A. M. Are fungus infections increasing as result of antibiotic therapy? *J. A. M. A.* **149**:979-983, 1952.
13. Negroni, P., and Daglio, C. A. N. Mycologic flora of sputum and their interpretation. *Prensa med. argent.* **35**:1450-1456, 1948.
14. Urso, B. Note on experimental bronchomoniliasis. *J. Trop. Med.* **54**:94-98, 1951.
15. Martin, D. S., Jones, C. P., Yao, K. F., and Lee, L. E., Jr. Practical classification of monilias. *J. Bact.* **34**:99-129, 1937.
16. Benham, R. W., and Hopkins, A. M. Yeast-like fungi found on skin and in intestines of normal subjects. *Arch. Dermat. & Syph.* **28**: 532-543, 1933.
17. Todd, R. L., and Hermann, W. N. Studies of yeast-like organisms isolated from mouth and throats of normal persons. *Am. J. Hyg.* **25**:212-220, 1937.
18. Knighton, H. I. Study of monilia and other yeast-like organisms found in oral cavity. *J. Dental Research* **18**:103-125, 1939.
19. Lilienthal, B. Studies of flora of mouth: yeast-like organism; some observations on their incidence in mouth. *Australian J. Exper. Biol. & M. Sc.* **28**:279-286, 1950.
20. Schnoor, T. F. Occurrence of monilia in normal stools. *Am. J. Trop. Med.* **19**:163-169, 1939.
21. Meads, M., Rowe, W. P., and Haslam, N. M. Alteration in bacterial flora of throat during oral therapy with aureomycin. *Arch. Int. Med.* **87**:533-540, 1951.
22. Parrott, R. H., McGovern, J. J., Ross, S., Rice, E. C., and Burke, F. G. Unpublished data.
23. Foley, G. E., and Winter, W. D., Jr. Increased mortality following penicillin of chick embryos infected with Candida albicans var. stellatoidea. *J. Infect. Dis.* **85**:268-274, 1949.
24. Levi, P. Research on action of antibiotics on pathogenic fungi. *Boll. d. Ist. sieroterap., milanese* **30**:168-175, 1951.
25. Seligman, E. Virulence enhancing activities of aureomycin on Candida albicans. *Proc. Soc. Exper. Biol. & Med.* **79**: 481-484, 1952.

MANAGEMENT OF BLEEDING FROM THE UPPER GASTROINTESTINAL TRACT*

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THERE have been two striking changes in the last twenty years in the management of hemorrhage from the upper gastrointestinal tract. Twenty years ago many able clinicians discouraged the giving of blood transfusions while bleeding was active. Today everyone advocates the early and liberal use of blood in any serious hemorrhage. The second change has been the recognition that surgery may have a place in the treatment of active bleeding. Twenty years ago few surgeons were permitted by their medical colleagues even to view a bleeding patient, for fear they might wish to operate.

What factors have led to this changing attitude toward surgery? A dispassionate review of hospital records shows that many persons with an open vessel in an ulcer actually die from hemorrhage that ought to be controllable by surgical means. Allen[1] was one of the first in this country to show a high fatality — about 1 in 3 — in patients over the age of fifty experiencing a massive hemorrhage from a duodenal ulcer; he urged a bolder surgical attack on these patients. Abroad, Finsterer,[2] in Vienna, and Gordon-Taylor,[3] in London, have long advocated such a view. The increasing availability of blood has made early treatment of the bleeding patient easier and better, and greatly increased the safety of surgical procedures by permitting massive transfusion for massive bleeding. Improved anesthetic technics, together with liberal blood transfusion, have allowed the surgeon to take critically ill patients into the operating room and perform with relative safety the formidable operations sometimes required. The demonstration by Hampton[4] and later by Schatzki[5] that diagnostic x-ray studies can be carefully and safely carried out on actively bleeding patients, made possible more accurate diagnosis before operation, leading to safer surgery. Probably of least consequence has been improvement in surgical technic.

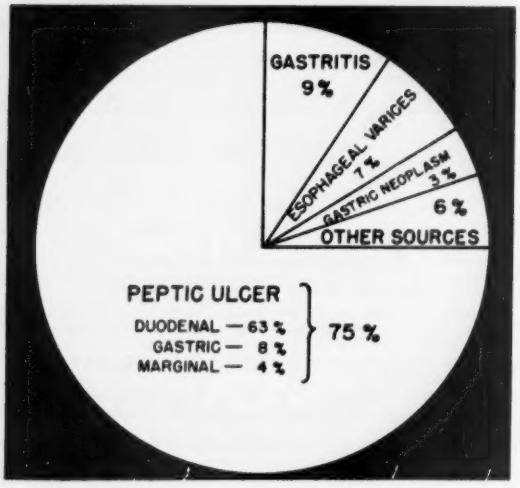

FIGURE 1. *Distribution of Lesions in Hemorrhage from the Upper Gastrointestinal Tract.*

What is the responsibility of the family physician who first sees a patient with hemorrhage from the upper gastrointestinal tract? It is assumed that other possibilities of bleeding — from the gums or nose and the respiratory tract — will first be ruled out. The physician can start with the knowledge that 75 per cent of these hemorrhages come from peptic ulceration — duodenal, gastric or jejunal ulcer, with gastritis and esophageal varices accounting for the bulk of the remainder (Fig. 1). In these days of therapy with ACTH and cortisone it may be expected that an even higher proportion of bleeding ulcers will appear, since these drugs stimulate the production of gastric juice and activate old ulcers or produce new ones.[6]

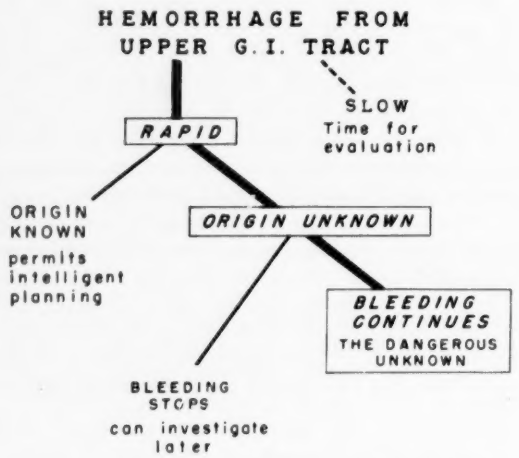

FIGURE 2. *Rate of Hemorrhage in Relation to Planning of Treatment.*

It may be helpful to consider the patient first from the standpoint of whether the hemorrhage is rapid or slow (Fig. 2). If bleeding is slow, there will be plenty of time for an accurate investigation

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and appraisal, whereas if it is rapid, vital decisions may have to be made promptly. If the physician knows the source of the hemorrhage from previous study, or if the history is so suggestive as to make a localizing diagnosis virtually certain, an intelligent and immediate appraisal is usually possible; even if such a patient is very ill, the decision to operate can be based on an exact diagnosis. The dangerous situation is posed by the patient who is bleeding from an unknown lesion, and in whom the hemorrhage is rapid.[7, 8]

How can one decide if the bleeding is rapid? Without in the least disparaging such valuable laboratory methods as blood-volume determinations, it is still safe to say that a bedside appraisal of the patient by the physician, using as his only instruments his brain and his five senses, usually answers the question of rapidity of bleeding almost as well as the more elaborate methods. A patient who is in peripheral vascular collapse, or who is bordering upon it, with pallor, cold and sweaty extremities, weak and rapid pulse, and anxiety, may immediately be assumed to be severely ill from rapid hemorrhage. Such a patient belongs in a hospital, and certain general measures applicable to all upper gastrointestinal hemorrhages should be promptly instituted. These include the liberal use of blood transfusion, bed rest and sedation as needed (usually phenobarbital rather than morphine, since intense pain is rarely a clinical feature of these hemorrhages). A careful medical ulcer regimen should be started at once (it will not hurt the patient who does not have an ulcer), and arrangements should be made for careful and continuous observation. The common denominator in various effective ulcer regimens is the hourly feeding so that there is always something in the stomach, frequent administration of an antacid and the use of antispasmodic drugs such as Banthine and atropine. Gastric suction is desirable only if there is persistent vomiting.

Again, although complicated laboratory tests may be useful in determining the continuation of a hemorrhage, they are beyond the reach of many physicians. However, the doctor can order a frequent determination of the blood pressure and pulse rate, and ask to be notified promptly if there is a significant drop in the first or a significant rise in the second. Uncompensated hemorrhage is almost always associated with an unstable circulation. The bleeding patient should be examined at least every eight hours; it can readily be determined whether he looks better or worse, and one can ask him how he feels. An improving patient will generally feel better. Determinations of the red-cell count, the hemoglobin or the hematocrit can be made every eight to twelve hours as a help in disclosing slow but persistent bleeding, which requires continuous transfusion. One may consider the applicability of certain special measures, which include placing the patient on constant urethral drainage to ensure that the urinary output is maintained despite continued hemorrhage, the possible use of esophageal tamponade[9] (if bleeding esophageal varices are suspected) and the oral administration of combinations of gelfoam, thrombin and buffer solution. The last device has been strongly recommended[10]; at worst, it can do no harm, although it is difficult to see how a really large, pumping, open artery will be affected by an orally administered coagulating agent.

The following types of cases are considered for possible emergency operation:

Patients over the age of fifty, who are closely followed from the start, because they may be bleeding from arteriosclerotic vessels that cannot easily contract or thrombose.

Patients who have been in peripheral vascular collapse — they are also watched closely, because the bleeding is presumably rapid.

If the circulation cannot be stabilized with several transfusions given in the first few hours, the bleeding is probably "surgical."

If rapid bleeding recurs after a quiescent interval, operation should be strongly considered, since it is in this type of patient that sudden and fatal exsanguination may take place.

If the hemorrhage exceeds a rate of 1500 cc. of blood a day, spontaneous recovery is unlikely.

Bleeding that is slow but persists for longer than two or three days may require a surgical operation (a forty-eight-hour deadline used to be widely respected by surgeons, who refused to operate upon patients if the hemorrhage had lasted longer, because the risk increased with the duration of the hemorrhage; today, in selected cases, operation is often undertaken after this forty-eight-hour limit, and many successful operations have been carried out a number of days after the first sign of a large hemorrhage).

Before an emergency operation is performed, certain criteria must be satisfied, or continued conservative management may be safer for the patient. There should be no constitutional contraindications, such as extreme obesity, decompensated heart disease and limited life expectancy because of some other disease. A patient should be constitutionally able to endure a general anesthetic, or continuous spinal anesthesia. (Attempts to do this type of surgery under local anesthesia are highly inadvisable, although successful cases have been reported.) Most surgeons demand the most experienced anesthetist available and wish to have at least 3 liters of blood ready for immediate use. Finally, esophageal varices as the cause of the bleeding must be excluded. It is best to know the exact source of the bleeding before the operation, but this is not always feasible. One may order emergency x-ray examination — to be done with consummate gentleness —

after the technic of Hampton[4] and Schatzki,[5] or an esophagoscopic study performed immediately before the laparotomy with the patient already anesthetized. If bleeding is from the esophagus, an emergency abdominal operation is valueless.

If the bleeding lesion is in the stomach — whether from an ulcer, a tumor or erosive gastritis — gastric

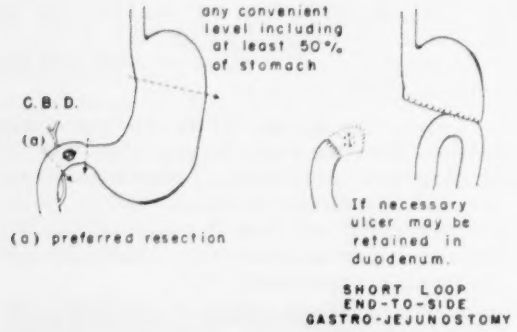

FIGURE 3. *Operation for Bleeding Duodenal Ulcer.*

resection including the lesion should be carried out. If the lesion is a duodenal ulcer, the bleeding vessel should be directly ligated in the ulcer bed, the duodenum turned in, and a gastric resection per-

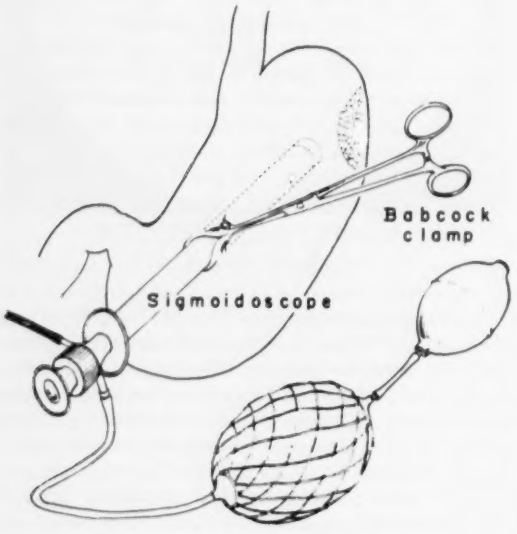

FIGURE 4. *Method of Gastroscopy at Time of Laparotomy.*

formed. If possible, the ulcer bed is excluded from the closed duodenum (Fig. 3). In an occasional case the maneuver recommended by Welch[11] may save time and possibly a life[12] — if the stump cannot be closed easily, a catheter is led out from the end of the duodenum, and no attempt is made to obtain a tight closure.

Occasionally, the surgeon cannot find an obvious lesion. He must then open the stomach and look inside. It may be helpful to utilize an ordinary sigmoidoscope, appropriately sterilized, inserted through a small gastrotomy, permitting air distention and inspection of the interior of the stomach (Fig. 4). In several cases it has been possible to detect ulcers or an erosive gastritis that could not otherwise be diagnosed, allowing a prompt and justifiable gastric resection. Some surgeons advocate a "blind" gastric resection if no lesion can be found, provided there is blood in the stomach. If no lesion can be demonstrated by transabdominal gastroscopy, it seems more logical to beat a retreat with the minimum of surgical trauma.

In the past seven years I have operated on 24 patients for active bleeding from the upper gastro-

TABLE 1. *Operations for Massive Hemorrhage from the Upper Gastrointestinal Tract.*

SOURCE OF BLEEDING	TOTAL NO. OF PATIENTS	PATIENTS WITH GASTRIC RESECTIONS	DEATHS
Duodenal ulcer	13*	12	1
Gastric ulcer	4	4	0
Jejunal ulcer	2	2	0
Gastric cancer	2	2	1
Gastritis	2†	1	0
Recent anastomosis (gastric resection on previous day)	1‡	0	0
Totals	24	21	2

*Vagotomy and posterior gastroenterostomy in 1 patient. This was an error in appraisal; there was no active bleeding at operation.

†Gastrotomy only in 1 patient.

‡Gastrotomy and ligature of bleeding vessel.

intestinal tract. Nearly all gave evidence of peripheral vascular collapse at some stage of the bleeding, and all gave evidence of severe continuing hemorrhage (Table 1). Nineteen patients bled from peptic ulcerations: 13 from duodenal ulcers, 4 from gastric ulcers, and 2 from jejunal ulcers. Two patients had erosive gastritis, 2 patients had gastric cancer, and 1 had had a gastric resection the day before. There were 2 deaths in this group. The first was the first patient in this series, a young man in his middle twenties who was bleeding from a duodenal ulcer; he died on the operating table after receiving more than 6 liters of blood. With a little more surgical skill this patient's life would have been saved; the bleeding was not controlled as promptly as it should have been. The second was a patient in his middle thirties who had a small ulcerative gastric carcinoma that bled so profusely that an emergency operation was performed at midnight. The carcinoma was a surprise finding. He died of liver failure in the third week after the operation, presumably from the massive metastases present in the liver; there were no technical errors connected with the operation itself. The patient

who bled profusely after a gastric resection deserves additional explanation. It is humiliating to the surgeon to have to reoperate upon a patient so soon after the original procedure, but this patient satisfied all the criteria for surgical intervention. He went into shock from hemorrhage, returns from the gastric suction made it clear that he was bleeding into his stomach, and he was still bleeding vigorously after he had received 3 liters of blood over a twelve-hour period. A large bleeding vessel

FIGURE 5. *Roentgenogram, Showing Filling Defect Produced by a Bleeding Leiomyoma in the Ileum.*

was found in the turned-in portion of the lesser curvature of the stomach (after a Hofmeister resection) that had somehow escaped the hemostatic suture. It is quite likely that this patient would have bled to death if the second operation had not been performed.

It is well known that the vast majority of patients recover from serious hemorrhages without surgical intervention. How should they be managed later? Every effort should be made to establish an accurate diagnosis. This may mean gastroscopic and small-bowel studies in addition to the usual x-ray examination of the esophagus, stomach and duodenum. It is often best to carry out these studies promptly after bleeding has ceased, since small ulcers sometimes heal rapidly. If one waits the ten to fourteen days formerly thought to be essential for safety and to avoid recurrence of the bleeding, one will have many diagnostic disappointments. A gastric ulcer or tumor should be eradicated by gastric resection. If the lesion is a duodenal ulcer, many sound clinicians believe that prolonged trial on nonoperative management is desirable, and they await a second or even a third hemorrhage in their younger patients before recommending an operation. This is justified on the basis that many patients are able to avoid an operation altogether. In older patients, on the other hand, a single serious hemorrhage from a duodenal ulcer should make one seriously consider the wisdom of definitive interval surgery. The choice of operation to be performed in the interval — whether a vagotomy with gastroenterostomy or a gastric resection — is beyond the scope of this paper. Some type of "appropriate" operation should be performed. If an erosive gastritis has been the cause of more than one serious hemorrhage, a gastric resection is probably advisable and has undoubtedly benefited some patients. If repeated x-ray examinations and gastroscopy fail to disclose a lesion, a surgical exploration should be advised in the presence of massive recurring hemorrhage. The surgeon sometimes finds and easily eradicates a benign tumor of the small intestine, usually a leiomyoma, which has been the source of the difficulty (Fig. 5 and 6). On

FIGURE 6. *Tumor Shown in Figure 3.*
The leiomyoma is dumb-bell shaped, half lying within the lumen of the ileum. The area of central necrosis can be seen.

the other hand, all surgeons have seen patients with recurrent, disabling hemorrhages in whom all x-ray studies have been repeatedly negative, and in whom one or more surgical explorations have failed to yield an answer. There is no known solution for the problem presented by such patients, particularly

since in some cases even the pathologist cannot demonstrate a bleeding point at post-mortem examination.

No discussion of hemorrhage from the upper gastrointestinal tract is complete without mention of the problem posed by bleeding esophageal varices. In active hemorrhage, esophageal tamponade with appropriate rubber balloons may be tried; some have reported enthusiastically on this procedure. The interval control, however, has brought forth a multiplicity of procedures, no one of which seems to be universally applicable. These procedures include operations designed to cut down portal-vein pressure, such as the various venous-shunt procedures, operations to cut down the collateral circulation varying from splenectomy to hepatic-artery ligation and operations designed to deal with the veins themselves, such as direct injection with sclerosing solutions and mediastinal packing. Esophagogastrectomy has been used to excise the veins and obliterate the collateral blood supply. Gastric resection has been performed in the hope that the trigger mechanism of a hemorrhage was ulceration from high gastric acidity. The place of each of these procedures will have to be determined by the test of time. Crile[13] has employed a direct obliteration of the varicosities in younger patients without liver damage, by opening the chest and the lower portion of the esophagus, and utilizing a continuous catgut over-and-over suture for the full length of the varix. Results have been encouraging in a small group of patients who have been followed for a minimum of three years.

Summary and Conclusions

The vast majority of patients experiencing a hemorrhage from the upper portion of the gastrointestinal tract get well on conservative measures including the liberal use of blood transfusions and a good ulcer regimen. Any operation needed by patients when hemorrhage subsides can be determined in an unhurried fashion and carried out during a quiescent interval. On the other hand, an occasional patient dies of hemorrhage from a curable lesion if a suitable operation is not carried out on an emergency basis. The family physician can select such patients for surgical consultation on the basis of a careful clinical appraisal; elaborate laboratory aids are unnecessary. The surgeon will wish to exclude esophageal varices as the source of the bleeding before undertaking a laparotomy for active hemorrhage. If no obvious lesion is found at operation a transabdominal gastroscopy may disclose the cause of the hemorrhage.

References

1. Allen, A. W., and Benedict, E. B. Acute massive haemorrhage from duodenal ulcer. *Ann. Surg.* **98**:736-749, 1933.
2. Finsterer, H. Surgical treatment of acute profuse gastric hemorrhages. *Surg., Gynec. & Obst.* **69**:291-298, 1939.
3. Gordon-Taylor, G. Problem of bleeding peptic ulcer. *Brit. J. Surg.* **25**:403-425, 1937.
4. Hampton, A. O. Safe method for roentgen demonstration of bleeding duodenal ulcer. *Am. J. Roentgenol.* **38**:565-570, 1937.
5. Schatzki, R. Roentgenologic examination of patients with bleeding from gastrointestinal tract. *New Eng. J. Med.* **235**:783-786, 1946.
6. Gray, S. J., Benson, J. A., Jr., Spiro, H. M., and Reifenstein, R. W. Effects of ACTH and cortisone upon stomach: its significance in normal and in peptic ulcer. *Gastroenterology* **19**:658, 1951.
7. Dunphy, J. E., and Hoerr, S. O. Indication for emergency operation in severe hemorrhage from gastric or duodenal ulcer. *Surgery* **24**: 231-238, 1948.
8. Hoerr, S. O., Dunphy, J. E., and Gray, S. J. Place of surgery in emergency treatment of acute massive upper gastrointestinal hemorrhage. *Surg., Gynec. & Obst.* **87**:338-342, 1948.
9. Rowntree, L. G., Zimmerman, E. F., Todd, M. H., and Ajac, J. Intraesophageal venous tamponade; its use in case of varical hemorrhage from esophagus. *J. A. M. A.* **135**:630, 1947.
10. Daly, B. M., Johnston, C. G., and Penberthy, G. C. Management of patients with bleeding from upper gastro-intestinal tract with buffer and thrombin solution. *Ann. Surg.* **129**:832-839, 1949.
11. Welch, C. E. Treatment of acute, massive gastroduodenal hemorrhage. *J. A. M. A.* **141**:1113-1119, 1949.
12. Hoerr, S. O., and Perryman, R. G. Catheter duodenostomy; safeguard in gastric resection: report of eleven cases. *Cleveland Clin. Quart.* **19**:49-56, 1952.
13. Crile, G., Jr. Transesophageal ligation of bleeding esophageal varices: preliminary report of seven cases. *Arch. Surg.* **61**:654-660, 1950.

THE PRECIPITIN TEST FOR BENCE-JONES PROTEIN*

Further Studies of Clinical Evaluation of the Test Employing Antibody Prepared by the Adjuvant Technic

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IN a previous communication[1] the need for a specific, sensitive test for Bence-Jones protein was stressed. The surprising infrequency with which positive findings for Bence-Jones protein are recorded lends weight to this concept. Of equal importance is the fact that the diagnosis of multiple myeloma, made frequently but late in the course of the disease, might be effected considerably earlier through employment of a more sensitive test for Bence-Jones protein, which, if present, is often the initial indicator of the fundamental pathologic process. A review of the hospital charts of 246 patients with diagnoses of multiple myeloma discloses a high percentage in whom, by virtue of evidence recorded, the suspicion of myeloma might have been entertained months or years sooner than the diagnosis was established. Diagnosis in retrospect, as this implies, is fraught with error, but the point is made in an effort to call attention to a pathologic process that is probably more common than generally realized and to urge employment of practical methods that will lead to early diagnosis. Definitive treatment of patients with multiple myeloma is at best equivocal; perhaps the generally poor results of treatment are due to the late timing of diagnosis.

The subject of this communication is an improved precipitin test for Bence-Jones protein. The first suggestion that Bence-Jones protein might be detectable by serologic means was made by Hektoen[2] in 1921. In this original work, untreated positive urine was used as the antigen, the rabbits being treated "intravenously every four or five days four or five times with increasing quantities of urine containing Bence-Jones protein." Positive ring-type precipitin tests were obtained when urine or serum containing Bence-Jones protein was placed in contact with antiserum prepared in this fashion. Work by Bayne-Jones et al.[3-5] indicated that "certainly two, possibly three groups of Bence-Jones proteins are recognizable by immunological tests." A similar conclusion was reached by Hektoen and Welker.[6] In the work of Bayne-Jones and his associates, 12 urine specimens from 5 patients were studied immunologically. The methods of isolation of protein from 3 of the specimens were described as "urine," indicating apparently that immunization was effected in a manner similar to that described by Hektoen. Protein from 3 specimens was isolated by precipitation with sodium sulfate and acetic acid, and protein from 4 specimens was isolated by coagulation by heat. It seems reasonable to suggest, then, that an alteration in the antigenic structure of the protein molecules might well account for the immunologic differences observed. Since three methods of isolation were employed, it is possible that this explains the "three groups of Bence-Jones proteins recognizable by immunological tests."

Later work[7] has shown antigenic similarity of samples of Bence-Jones protein from 4 patients. The antiserums used in this work were produced in rabbits, by immunization with purified precipitates of Bence-Jones protein, rather than unmodified urine, as was done in Hektoen's original work.

Routine chemical tests of urine for Bence-Jones protein too frequently fail to reveal this protein if it is present in low concentration. In this laboratory, chemical tests have failed to demonstrate the presence of the redissolved crystalline protein in concentrations less than 0.36 gm. per 100 cc. The most optimistic report of the incidence of Bence-Jones protein in the urine of patients with multiple myeloma is the statement of Geschickter and Copeland,[8] who found the protein present in 65 per cent of cases. They further state:

> Repeated statements in the literature cite the incidence of Bence-Jones bodies as 80% for all cases. Search for. . . evidence failed to disclose its source.

It is probable that Bence-Jones protein is found in the urine by chemical tests in about 50 per cent of patients with multiple myeloma. Bayrd and Heck[9] report an incidence of 53 per cent in patients with multiple myeloma; Brunsting and MacDonald[10] mention an incidence of 44 per cent in patients with multiple myeloma and primary systematized amyloidosis. In this laboratory repeated tests on urine negative for Bence-Jones protein have been observed to be positive after concentration of the urine by cold dehydration in a semipermeable membrane. This indicates that the excretion of Bence-Jones protein by patients with multiple myeloma occurs somewhat more frequently than is generally credited and that the relative infrequency with which chemical tests disclose the presence of the protein is a

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measure of the inadequacy of the tests, rather than the rarity of the protein. Even electrophoresis and ultracentrifugation fail to reveal the protein if it is present in concentrations less than 0.1 gm. per 100 cc. Since some precipitin tests are capable of demonstrating the unknown in dilutions as high as 0.0001 gm. per 100 cc., it was thought that antibody to Bence-Jones protein might be employed in such a precipitin test to detect the protein in urine specimens negative to the routinely employed chemical tests.

Methods and Materials

Fresh urine specimens were obtained from 6 patients in whom the diagnosis of multiple myeloma had been established by morphologic and cytologic observations on smears obtained from sternal or iliac bone marrow. Specimens from these particular patients were selected for two reasons: the relatively heavy Bence-Jones protein; and the extremely low concentration of albumin in the urine as shown by routine chemical tests. The hydrogen ion concentration of each specimen was adjusted

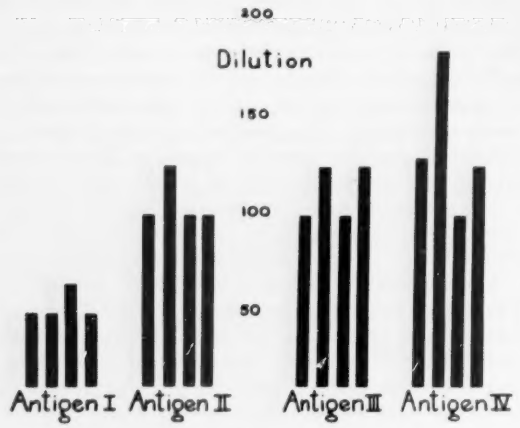

Figure 1. *Homologous Antigen-Antibody Titrations with the Intravenous Technic (Employing Titer Reciprocal of Dilution).*

to a pH of 5.0, and at 4°C. 40 gm. of sodium chloride was added to each 100 cc. of urine. Many technics are available for the precipitation of Bence-Jones protein, but this was considered to be the least likely to alter the antigenic structure of the protein. Dialysis of the precipitates thus formed was effected in distilled water, until the dialysates were demonstrated to be chloride free. In this assay the chloride ion was used as an indicator, and it was believed that when the antigenic material was free from this ion, it would also be devoid of other dialyzable substances that might prove toxic on injection. The purified protein precipitates were then lyophilized at 4°C. and employed as antigens. Each of four of the purified protein precipitates was prepared as a 20 per cent suspension in physiologic saline solution and administered intravenously to each of 4 rabbits. It was not possible to obtain titers higher than 1:180 after four courses of one week of daily immunization followed by one week of rest (Fig. 1).

It was believed that the low antigenicity of Bence-Jones protein might be intensified by the use of the adjuvant technic suggested by Dienes[11, 12] and developed by Freund and McDermott.[13] Two of the lyophilized purified protein precipitates were modified by Freund's adjuvant, and, again, each of the antigens was injected into 4 rabbits. Forty milli-

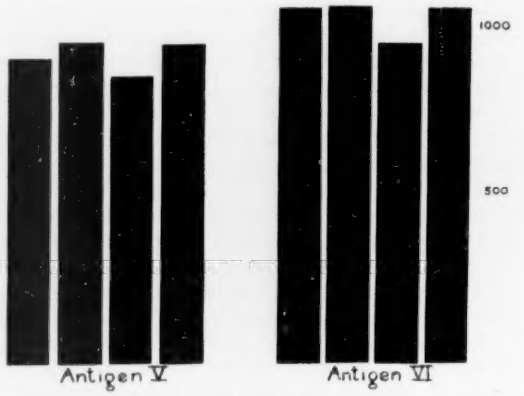

Figure 2. *Homologous Antigen-Antibody Titration with the Adjuvant Technic (Employing Titer Reciprocal of Dilution).*

grams of *Mycobacterium phlei* ("timothy bacillus") was heated to 100°C. for an hour; 30 cc. of paraffin oil and 10 gm. of Aquaphor were mixed and autoclaved for thirty minutes, 2 gm. of the lyophilized Bence-Jones protein then being added to the mixture of paraffin oil, Aquaphor and killed acid-fast organisms. A single intramuscular injection of 5 cc. of this antigen adjuvant, accompanied by a single intramuscular injection of 5 cc. of 20 per cent suspension of purified antigen, produced in four-week rabbit antiserums with maximum precipitin titers of 1:1050 (Fig. 2). The advantage of the adjuvant technic in inducing immune response to Bence-Jones protein, is clearly shown by a comparison between homologous antigen-antibody titrations of intravenously injected saline antigen, and antigen modified by Freund's adjuvant (Fig. 3). Previous studies[7] had demonstrated the existence of cross-precipitin reactions in heterologous antigen-antibody studies of samples of Bence-Jones proteins obtained from four patients. The heterologous antigen-antibody titrations conducted in the current study demonstrated two features: corroboration of the previously shown cross-precipitin reactions, and the superior "precipitating ability" of

antiserums prepared by the adjuvant technic (Fig. 4).

Repeated demonstrations of cross-precipitin reactions of several different samples of Bence-Jones protein tend to confirm the original impression of the antigenic similarity — if, indeed, not antigenic identity — of the products studied. This obviously

FIGURE 3. *Homologous Antigen-Antibody Titration (Maximum Titer).*

Blocks numbered 1, 2, 3 and 4 represent antibody prepared by intravenous technic, and those numbered 5 and 6 antibody prepared by adjuvant technic.

does not imply actual identity, physical or chemical, of the proteins studied, but, by virtue of antigenic similarity, it was believed that there was definite diagnostic value in the antiserums. The ability to

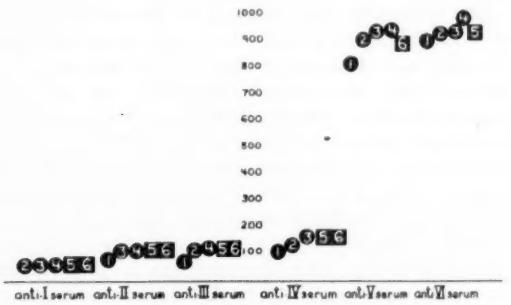

FIGURE 4. *Heterologous Antigen-Antibody Titration, Showing Mean Titrations Obtained with Intravenous (Circles) and Adjuvant Technics (Squares).*

produce antiserums in relatively high titers made possible clinical tests of this product.

PRECIPITIN TEST FOR BENCE-JONES PROTEIN

The demonstration of cross-precipitin reactions rendered the high-titered antiserums of value in diagnosis, and a simple precipitin test for Bence-Jones protein was instituted, employing patients' urine and antiserums prepared by the adjuvant technic. The pH of the urine to be tested was adjusted to neutrality, and the specimen centrifuged at 3800 G. Immediately before the test, the antiserum was also centrifuged at 3800 G. In a small test tube an interface was formed by the overlaying of 0.1 cc. of the supernatant from the urine with 0.2 cc. of the antiserum. Three simultaneously performed controls were instituted in which both urine and antiserum were submitted to procedures identical to those in the test situation. The first control tube contained immune rabbit serum and urine in which the chemical test for Bence-Jones protein had been positive, the second contained immune rabbit serum and urine from a normal subject, negative for Bence-Jones protein, and the last

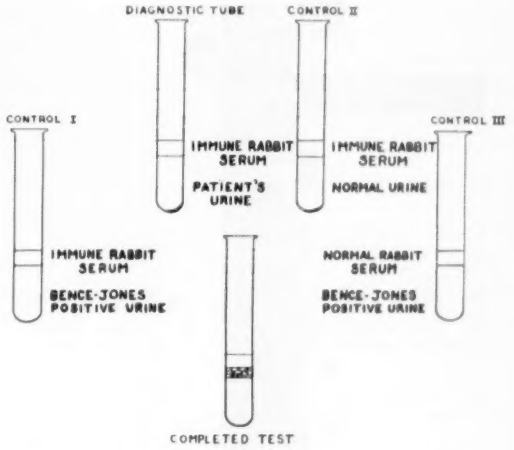

FIGURE 5. *Precipitin Test for Bence-Jones Protein.*

contained normal rabbit serum and urine known to be Bence-Jones positive (Fig. 5).

After the urine supernatant had been overlaid with the appropriate serum, the four tubes were incubated at 37°C. for an hour and then refrigerated overnight. Cryoglobulins had not been found in any of the rabbit serums, normal or immune, but to obviate false-positive reactions due to cryoglobulins that might have passed through the glomeruli and appeared in the test urine, the tubes were allowed to assume room temperature before interpretation of the test. The presence of a true precipitate at the interface in the test with the unknown specimen was regarded as positive if a precipitate was observed in the positive control while none was found in either of the negative controls. It should be noted that on many occasions, precipitates were noted in the test and positive control tubes shortly after the serum had been placed over the urine supernatant; it was considered necessary to incubate and fix at refrigeration temperatures even when such early precipitates were found, to rule out false-positive reactions.

Clinical Evaluation

Evaluation of urine specimens from 1000 different persons was carried out by means of the precipitin test for Bence-Jones protein. Tests on 57 of these patients met the criteria for positivity (Fig. 6). Of these, 53 were patients with the diagnosis of multiple myeloma. In 20 of these cases diagnosis had been established before employment of the precipitin test; of these, Bence-Jones protein was detected in the urine by chemical tests incident to diagnosis in 11. Of the remaining 42 patients, none had chemically detected Bence-Jones proteinuria before diagnosis. Thirty-three of the cases of myeloma were undiagnosed before the serologic test for Bence-Jones proteinuria, and the findings were of diagnostic import. Thus, the serologic test was the first positive laboratory finding pointing to the diagnosis in a little over 62 per cent of the patients with myeloma in this series. Negative chemical tests with positive serologic tests were recorded on 3 patients in whom subsequent laparotomies disclosed so-called "solitary plasmacytomas." A similar situation was found in a patient whose final diagnosis was acute lymphatic leukemia; it should be noted here that some observers thought this case represented a plasma-cell leukemia, rather than lymphatic leukemia. Negative tests, serologic and chemical, for Bence-Jones protein were recorded on 158 normal controls recruited from the laboratory and house staffs. Urine specimens from 608 random patients, examined in sequence on admission, without regard for disease or complaint, were also negative to both tests. Specimens from 179 patients with previously diagnosed leukemia were tested chemically and serologically for Bence-Jones protein during the eighteen-month study. Only in the single case discussed above was a positive serologic but negative chemical test recorded. Of the remaining patients with leukemia, diagnoses had been established for 52 patients with acute myeloid leukemia, 30 with chronic myeloid leukemia, 51 with acute lymphatic leukemia, 30 with chronic lymphatic leukemia, 10 with acute monocytic leukemia and 4 with "leukolymphosarcoma."

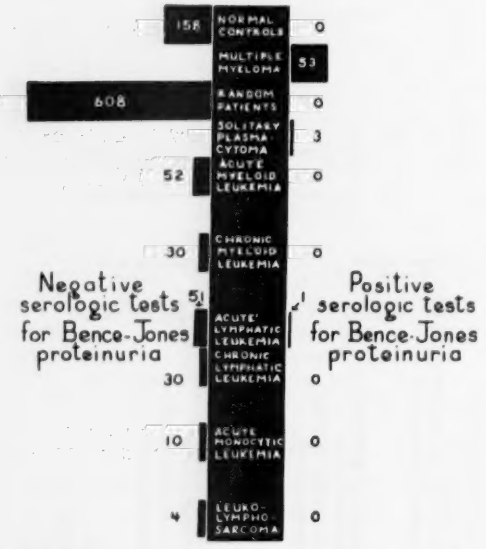

Figure 6. *Clinical Application of Test for Bence-Jones Protein.*

Discussion

Although Bence-Jones protein has excited interest in the medical profession for over a hundred years, the academic literature contains many conflicting reports concerning, particularly, the following three aspects of this substance: a precise definition of the protein; the incidence of its occurrence in patients with multiple myeloma; and the question of its appearance in the urine of patients with other diseases.

In this series of studies we have accepted the definition of Bence-Jones protein as a urinary protein with a mean molecular weight of 37,000 (representing variations from 24 to 90,000), showing the peculiar thermal precipitative qualities originally ascribed to the substance by Sir Henry Bence-Jones.[14] Rundles et al.[15] have furthered the concept that Bence-Jones protein represents an alteration in the abnormal serum proteins seen in multiple myeloma.

The figures on the incidence of Bence-Jones protein in the urine of patients with myeloma are quite variable, but it seems reasonable to assume that chemical tests are positive in a little over half the patients at some stage of the disease. It seems from the present work that this figure is a reflection of the inadequacies of chemical tests for detecting the protein when it is present in low concentrations. The serologic test for Bence-Jones protein has shown a higher correlation between the presence of this substance in the urine and multiple myeloma than has previously been noted. In this series, barring the presence of false-negative tests (of which none are suspected), the correlation has been exceedingly close to absolute.

The question of appearance of Bence-Jones protein in the urine of patients with diseases other than those in the general group of plasma-cell tumors — myeloma or plasmacytoma— is such as to stimulate investigative work to lead to a definitive answer. The finding of Bence-Jones protein in the urine of a patient with lymphatic leukemia was of interest to us because, if the final diagnosis was correct, it afforded an opportunity for personal observation of such a rare case.

The electrophoretic apparatus and the ultracentrifuge were not available to us during the greater

part of this study. Therefore, no data from these sources have been included. As previously pointed out[16] the addition of the immunologic technics to those of electrophoresis and ultracentrifugation shows promise in the elucidation of the nature of Bence-Jones protein, physically, chemically and immunologically. A valid discussion of the common denominators of Bence-Jones protein must await further integrating work with these three technics.

Serologic evaluations of different specimens from the same person were relatively constant from the qualitative aspect. Quantitative estimations, as might have been expected, showed variations in the amounts of protein excreted at different stages of the disease. The greatest interval afforded for repeated tests on urine specimens from a patient with positive serologic tests has been seventeen months. In the 57 patients studied who showed initially positive precipitin tests for Bence-Jones protein, it was found that all subsequent serologic tests were positive. In 3 patients in whom initial chemical tests were negative while serologic tests were positive, subsequent routine chemical tests were positive. In 1 of these, only four subsequent urine specimens were positive to the chemical tests, after which the specimens reverted to chemical negativity with concurrent serologic positivity. This situation obtained immediately before the patient's death. It should be stressed that in many of the urine specimens that were negative to the chemical test for Bence-Jones protein but positive by serologic test, concentration of the urine by cold dehydration in a semipermeable membrane permitted the demonstration of positive chemical tests for the protein.

Immune serum, specific for human gamma globulin, did not precipitate any of the antigens employed in this study. Conversely, immune serums to the six Bence-Jones proteins studied, failed to precipitate normal human gamma globulin.

Antiserum prepared by the adjuvant modification of immunization to Bence-Jones protein was employed in testing for redissolved crystalline Bence-Jones protein prepared in serial dilutions. Positive ring-type precipitin tests were found in dilutions as great as 0.007 gm. per 100 cc.

These data showed the value of the precipitin test in the discovery of Bence-Jones protein in low concentration. Therein, however, lies one of the criticisms that theoretically must be levied against the test — namely, that the high sensitivity might be regarded as making the test results somewhat less significant than would be desirable. The fact that no false-positive tests have been recorded in these series should militate against this criticism. Another point that merits discussion — the antigenic specificity of Bence-Jones protein — has been under debate for some years. The cross-precipitin reactions observed in heterologous antigen-antibody titrations lend weight to the statement that the six specimens studied were antigenically similar. If the term, "Bence-Jones protein," is regarded as embracing a number of proteins, different in physical, chemical and immunologic properties, the question must be raised of specificity of such a test as is here described. Obviously, the problem of false-negative tests must be considered in the 943 persons whose urine failed to react with the antiserum. It is within the realm of limited possibility, statistically, that 1 of these subjects could exhibit Bence-Jones protein that is not detected by the chemical or serologic tests. Adequate follow-up studies on these persons should show whether the tests, recorded as negative, were truly accurate. In more than 80 per cent there were no clinical findings to warrant suspicion of Bence-Jones protein in the urine, and it seems reasonable to assume that no false-negative results were obtained. Finally, it seems obvious that the use of adequate controls should demonstrate the selectivity and sensitivity of the test to be equally high.

Summary and Conclusions

The need for earlier diagnosis of multiple myeloma is stressed.

It is believed that a valuable adjunct to early diagnosis is the development of a precipitin test for Bence-Jones protein, capable of detecting the protein in the urine at an early stage of the disease when the urinary protein concentration is usually relatively low.

Earlier diagnosis should afford more ample opportunity for clinical study of the disease and therefore, indirectly, be of therapeutic aid.

A technic is described in which the addition of Freund's adjuvant to precipitated, purified, lyophilized Bence-Jones protein induces sufficient immune response in rabbits to make the antiserum suitable for clinical tests.

The consistent demonstration of cross-precipitin reactions in heterologous antigen-antibody reactions points to antigenic similarity of the six proteins studied and warrants the use of the antiserum in clinical diagnosis.

Urine specimens from 1000 persons were studied by the precipitin technic, employing antiserums prepared by the use of Freund's adjuvant. Fifty-seven positive tests were recorded; their significance is discussed.

Absence of false-positive tests, failure to precipitate normal human gamma globulin with the antiserums and failure to precipitate the purified Bence-Jones protein with antihuman gamma globulin are interpreted as showing the antigenic specificity of the proteins studied and the value of the test.

The test was of diagnostic aid in establishing the diagnosis of plasma-cell overgrowth (multiple myeloma or plasmacytoma) in 36 of 56 patients with these disorders.

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References

1. Collier, F. C., Reich, A., and King, J. W. Multiple myeloma: report of four cases demonstrating Bence-Jones proteinemia found during routine complement-fixation tests. *New Eng. J. Med.* **245**:969-971, 1951.
2. Hektoen, L. Specific precipitin for Bence-Jones protein. *J. A. M. A.* **76**:929, 1921.
3. Bayne-Jones, S., and Wilson, D. W. Immunological reactions of Bence-Jones proteins. I. Differences between Bence-Jones proteins and human serum proteins. *Bull. Johns Hopkins Hosp.* **33**: 37-43, 1922.
4. *Idem.* Immunological reactions of Bence-Jones proteins. II. Differences between Bence-Jones proteins from various sources. *Bull. Johns Hopkins Hosp.* **33**:119-125, 1922.
5. Everett, H. S., Bayne-Jones, S., and Wilson, D. W. Precipitin reactions of crystalline globulin from human urine. *Bull. Johns Hopkins Hosp.* **34**:385-387, 1923.
6. Hektoen, L., and Welker, W. H. Immunological differences of crystalline Bence-Jones proteins. *Biochem. J.* **34**:487-489, 1940.
7. Collier, F. C., Reich, A., and King, J. W. Value of precipitin tests for Bence-Jones protein in early diagnosis. *New Eng. J. Med.* **247**: 22-24, 1952.
8. Geschickter, C. S., and Copeland, M. M. *Tumors of Bone.* Third edition. 810 pp. Philadelphia: Lippincott, 1949.
9. Bayrd, E. D., and Heck, F. J. Multiple myeloma: review of eighty-three proved cases. *J. A. M. A.* **133**:147-157, 1947.
10. Brunsting, L. A., and MacDonald, I. D. Primary systematized amyloidosis with macroglossia: syndrome related to Bence-Jones proteinuria and myeloma. *J. Invest. Dermat.* **8**:145-165, 1947.
11. Dienes, L., and Schoenheit, E. W. Reproduction of tuberculin hypersensitiveness in guinea pigs with various protein substances. *Am. Rev. Tuberc.* **20**:92-105, 1929.
12. *Idem.* Certain characteristics of infectious processes in connection with influence exerted on immunity response. *J. Immunol.* **19**:41-61, 1930.
13. Freund, J., and McDermott, K. Sensitization to horse serum by means of adjuvants. *Proc. Soc. Exper. Biol. & Med.* **49**:548-553, 1942.
14. Bence-Jones, H. On new substance occurring in urine of patient with mollities ossium. *Phil. Tr. Roy. Soc., London* 55-62, 1848.
15. Rundles, R. W., Cooper, G. R., and Willett, R. W. Multiple myeloma. IV. Abnormal serum components and Bence-Jones protein. *J. Clin. Investigation* **30**:1125-1142, 1951.
16. Moore, D. H., Kabat, E. A., and Gutman, A. B. Bence-Jones proteinemia in multiple myeloma. *J. Clin. Investigation* **22**:67-75, 1943.

MEDICAL PROGRESS

PHARMACOLOGIC ASPECTS OF ADRENOCORTICAL STEROIDS AND ACTH IN MAN (Continued)*

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BOSTON

Preparations and Routes of Administration

Cortisone is supplied for therapeutic use in the form of the acetate ester. Four preparations are currently available: tablets for oral administration containing 5 or 25 mg. of cortisone acetate; a microcrystalline suspension of cortisone acetate in physiologic saline solution for intramuscular injection containing 25 or 50 mg. per cubic centimeter — minute quantities of suspending agents (such as polyoxyethylene sorbitan mono-oleate and sodium carboxymethylcellulose) and a preservative (for example, 1.5 per cent benzyl alcohol) are also present; a microcrystalline suspension of cortisone acetate in a solution of phosphate buffer for ophthalmic (topical) use, containing 5 or 25 mg. per cubic centimeter, with 0.5 per cent benzyl alcohol and 0.02 per cent Zephiran Chloride as preservatives; and an ophthalmic ointment containing 1.5 per cent cortisone acetate in a petrolatum base.

Solutions of cortisone suitable for continuous intravenous administration have recently been prepared in this laboratory,[416] the nonacetylated (free alcohol) compound being used since it has not been possible to date to prepare a satisfactory solution of cortisone acetate for intravenous use. The following method of formulation has been employed: a sterile, aqueous suspension of cortisone (*free alcohol*) containing 25 mg. per cubic centimeter is added to sterile 95 per cent ethyl alcohol and sterile water, in the order given, in the proportions of 4 cc. of steroid suspension, 6 cc. of alcohol, and 4 cc. of water. This solution is immediately diluted to any desired volume in physiologic saline solution or 5 per cent dextrose in water for intravenous infusion. If aqueous suspensions of the steroid are unavailable, satisfactory solutions may be prepared from crystalline cortisone, a known quantity of sterile cortisone (free alcohol) being dissolved by vigorous shaking in 80 per cent ethyl alcohol in the proportions of 10 mg. per cubic centimeter. This solution is then injected *rapidly* into the desired volume of saline or dextrose diluent for intravenous infusion. No untoward effects have been observed from the relatively small quantity of alcohol used. The administration of 100 mg. of cortisone dissolved in 500 cc. of saline or dextrose solution by continuous

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intravenous infusion over a period of eight hours or longer has been demonstrated to produce metabolic changes of nearly maximal intensity.[417]

Cortisone is ordinarily administered for therapeutic purposes by either the intramuscular or the oral route. In addition, the hormone has been infused intravenously, dropped into the conjunctival sac and injected directly into accessible body spaces, including joints, bursas and the pleural, peritoneal and pericardial compartments. The hormone has been rubbed onto the skin in ointments and solutions, implanted under the skin in the form of pellets and sprayed into the upper respiratory tract as an aerosol. Such a diversity of routes reflects the attempt to modify, largely by restriction of hormonal activity to specific areas, the generalized metabolic effects obtained with systemic administration.

The first preparation of cortisone available for general clinical use was the microcrystalline suspension in physiologic saline solution for intramuscular injection. Dissolution of the intramuscular deposit of steroid crystals proceeds so slowly that the blood levels of free corticosteroid are usually only moderately elevated.[385] Consequently, the effective duration of a single dose ordinarily extends over a period of twenty-four hours or slightly longer. Although the peak activity of a single dose usually occurs between eight and twelve hours after intramuscular injection, both metabolic and clinical effects are often evident within three or four hours. To obtain a rapid and sustained level of maximal activity, the hormone is ordinarily administered at intervals of eight to twelve hours; for maintenance therapy, however, a single injection during each twenty-four-hour period is ordinarily sufficient. After prolonged intramuscular administration of large doses of cortisone acetate, cumulation of the hormone is evidenced by a persistence of effects for several days after the discontinuation of injections.

Evidence for the adequate absorption of orally given cortisone acetate has been cited above. The clinical[384] and metabolic[250] effectiveness of cortisone acetate administered by this route has been well documented. It has repeatedly been demonstrated in man that the over-all metabolic and therapeutic effects of equivalent daily doses of orally and intramuscularly administered cortisone acetate are not strikingly different. The clinical dosage-equivalence ratio of orally to intramuscularly given hormone has, in most cases, ranged between 1.0 and 1.5.

The effects of cortisone acetate given intramuscularly and by mouth differ chiefly in their time-response relations. This is well illustrated by a comparison of changes in circulating eosinophils elicited by single doses of the hormone in patients with Addison's disease, in whom variations in endogenous corticosteroid secretion do not influence the evaluation of results. The maximal effect of cortisone by mouth is obtained within four to eight hours and rapidly declines. In contrast, the eosinopenic action of intramuscularly injected cortisone acetate at this dosage level is not only much less intense but also markedly delayed, undoubtedly reflecting a slow absorption rate. Even with continued daily intramuscular injections of 100 to 200 mg., eosinopenia may not be pronounced until the cumulative actions of the intramuscular depots become apparent.

Similar differences between the two routes are well delineated by a comparison of the effects on urinary electrolyte excretion of equivalent dosages of intramuscularly and orally administered corti-

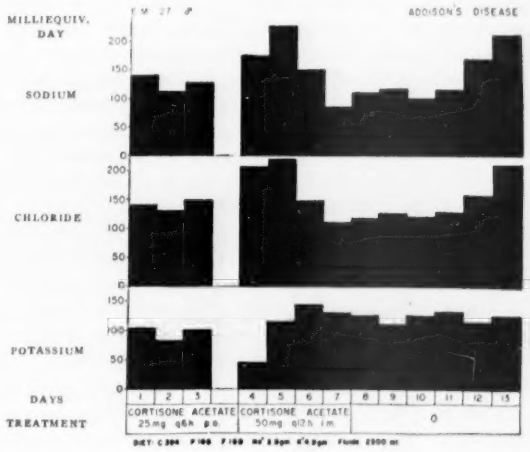

FIGURE 20. *Comparison of Effect of Oral and Intramuscular Administration of Cortisone on Renal Excretion of Electrolyte. (Reproduced from Thorn et al.*[250]*).*

The periods of oral and intramuscular administration were consecutive.

sone acetate in a patient with Addison's disease (Fig. 20). Upon substitution of intramuscular cortisone acetate for an equivalent total daily dose of orally administered hormone, a prompt rise in sodium and chloride excretion and a significant fall in urinary potassium indicated a rapid disappearance of the effects of the oral preparation. In addition, the onset of effective electrolyte control was delayed until the third day of intramuscular administration, and the action persisted through the fifth day after the last injection of steroid. The delayed cumulative effects of intramuscularly administered cortisone acetate and the persistence of activity after the final injection contrast with the more rapid and intense but relatively brief action of the preparation given orally. It appears, however, that the intramuscular preparation is somewhat more effective in its electrolyte-regulating capacity, once maximal activity is reached, than the orally

administered hormone. It is probable that this difference is attributable to the sustained effect on renal function of a relatively slow but continuous absorption of cortisone.

A further disparity between the effects of oral and intramuscular administration of the hormone deserves emphasis. Wilkins et al.[81] have well demonstrated that intramuscularly injected cortisone acetate, despite a delay in onset of action, is considerably more efficient than an equivalent quantity of steroid administered orally in the suppression of adrenocortical activity in patients with congenital adrenal hyperplasia. Experience in this clinic indicates that this finding applies equally well to patients with normal adrenocortical function. These observations suggest that the release of cortisone acetate from intramuscular depots more effectively inhibits the output of ACTH from the anterior pituitary body than the intermittent activity of orally administered hormone. It seems evident that differences in time-response relations between these two systemic routes of hormone administration, as well as quantitative differences in certain metabolic actions, can be attributed to the marked disparity in the rate of hormone absorption.

It is therefore apparent that the oral use of cortisone acetate in clinical therapy requires frequent administration. In most cases the therapeutic effectiveness of cortisone acetate given orally at six-hour intervals is approximately equal to that of intramuscular injection once daily. Furthermore, its rapidity of action makes the oral administration of cortisone acetate preferable to intramuscular injection in acute conditions requiring immediate high levels of circulating corticosteroid. Although the absence of a prolonged effect after cessation of oral therapy materially lessens the hazard of persistent hormonal action in patients with serious signs of steroid overdosage, it must be emphasized that this rapid decline in hormonal action may, in the presence of effective pituitary-adrenal inhibition, rapidly project the patient into an acute state of relative adrenal insufficiency. The comparatively slow decline of accumulated intramuscular depots of hormone, on the other hand, tends to prevent this unfortunate sequel of prolonged administration.

Cortisone acetate pellets have been employed for the long-term substitution therapy of patients with Addison's disease.[101] The optimum pellet weight was found to be between 1.0 and 1.5 gm. per implant. The average daily dissolution was approximately 10 mg. of hormone a day. The duration of clinical effectiveness of a single implant averaged four or five months. Although the effects of this form of therapy were identical to those observed after cortisone given either intramuscularly or orally, the latter routes of administration are preferable for general clinical use. Henderson et al.[418] have recently described the use of cortisone acetate pellets in the maintenance treatment of patients with rheumatoid arthritis. The pellet implantation is apparently feasible only in patients whose daily hormone requirement is very small.

The administration of cortisone intravenously obviously constitutes the method of choice in situations requiring an immediate and sustained high level of circulating corticosteroid. The principle therapeutic advantage of this route lies in the speed with which metabolic effects of maximal intensity are produced. Moreover, large quantities of cortisone can be rapidly administered to patients who are unconscious or in whom oral medication is precluded. Thus, in patients in acute Addisonian crisis or in cases of surgical emergency intravenous therapy is clearly the procedure of choice.

Cortisone acetate has been extensively used by local administration only in the treatment of inflammatory eye diseases.[419] Topical therapy is economical, far less of the hormone being required than in systemic administration. In addition, effective steroid concentrations may be achieved without undesirable systemic effects. This route has proved effective chiefly in diseases of the anterior segment; disorders of the posterior segment are ordinarily more effectively treated by parenteral administration. Topical application has been especially helpful in the relief of pain and photophobia associated with corneal lesions. Leopold et al.[420] have presented evidence of effective penetration of the hormone into intraocular fluids.

Two concentrations of ophthalmic suspension are available (0.5 per cent and 2.5 per cent), the choice depending largely on the severity of the inflammatory reaction to be treated. In acute, severe disease treatment is often initiated with the more concentrated preparation. Maintenance therapy may then be continued with the dilute suspension. The most widely employed therapeutic program consists of the administration of 1 or 2 drops of suspension every hour during waking hours and every two hours at night.[421] When control of the disease has been established, dosage may be reduced to 1 drop every four hours or even four times daily. In cases requiring an eye pad, the ophthalmic ointment may be more conveniently applied than the suspension. The ointment is also useful for nocturnal application. Cortisone acetate has been administered subconjunctivally,[422] 0.05 to 0.4 cc. of the saline suspension being injected under local anesthesia. The deposit remains beneath the conjunctiva for several days, with a repository effect. No contraindications to the topical use of cortisone acetate have been described, with the exception of ocular tuberculosis.

Cortisone acetate has been administered locally by injection into inflamed joints without therapeutic effects approaching those achieved with hydrocortisone.[231] The hormone has been aerosolized for administration by inhalation in patients with bronchial asthma.[423] Therapeutic benefit was compara-

tively slow to appear, and, aside from the absence of undesirable systemic effects, the method appears to offer no real advantage over oral or parenteral administration. Cortisone acetate has been applied locally to the skin in patients with chronic discoid lupus erythematosus[424] and other dermatologic disorders, with only moderate clinical improvement. Again, it appears that hydrocortisone is considerably more effective than cortisone after inunction.

HYDROCORTISONE

Hydrocortisone, or Compound F (Fig. 21) was first isolated from adrenocortical extracts in 1937 by Reichstein[71] and Mason et al.[425] Subsequently, this compound was shown to be more active than

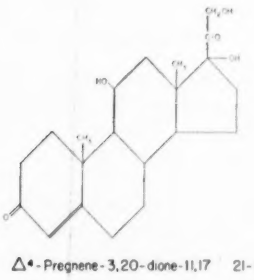

FIGURE 21. *Chemical Structure of Hydrocortisone (17-Hydrocorticosterone, Compound F).*

either cortisone or corticosterone in the work performance of adrenalectomized rats,[426] in the glycogenic test in adrenalectomized rats[427] and in its diabetogenic action and antianabolic effect on protein in force-fed normal rats.[221] In 1948 the isolation of hydrocortisone from the urine of a patient with Cushing's syndrome by Mason and Sprague[428] provided direct evidence concerning the chemical nature of a steroid hormone produced by the adrenal cortex. This isolation and the discovery of the potent anti-inflammatory effects of cortisone in 1949[102] led to a reawakening of interest in hydrocortisone, and in 1950 Hench and his associates[102] reported the beneficial effects of this hormone in rheumatoid arthritis. In 1950 the partial chemical synthesis of hydrocortisone was first reported.[429] Subsequently, hydrocortisone has assumed increasing importance with the discovery that it is the principal corticoid in adrenal-gland perfusates,[4] adrenal venous blood[391, 394] and peripheral blood.[392] These findings have led to the view that hydrocortisone is the principal hormone secreted by the adrenal cortex.

PHYSIOLOGIC ACTIONS

Quantities of hydrocortisone sufficient for general use have only recently become available. It is already quite apparent that most of the major metabolic and therapeutic actions of cortisone and hydrocortisone are similar. Certain important differences have already been demonstrated, however, and are pertinent to any comparative evaluation of the two steroids.

Early physiologic studies with hydrocortisone, administered by intermittent intramuscular or subcutaneous injection, demonstrated, by various criteria, that this hormone possessed greater metabolic activity than cortisone.[221, 426, 427] That the difference in potency was not due to differences in either the rate of absorption or speed of inactivation has been unequivocally demonstrated by the studies of Ingle and his co-workers,[430] in which the hormones were administered by continuous intravenous infusion and assayed by the muscle-work test. Hydrocortisone was found to be approximately twice as effective as cortisone. Comparative studies in man, employing the intravenous route of administration, have confirmed the greater potency of hydrocortisone.[416] This is demonstrated in Figure 22, which shows the eosinopenic effect of free hydrocortisone

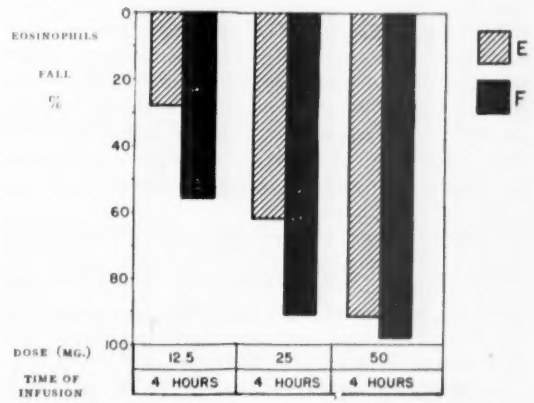

FIGURE 22. *Eosinophil Response to the Intravenous Administration of Cortisone (E) and Hydrocortisone (F) in a Thirty-Three-Year-Old Man with Addison's Disease.*

Cortisone and hydrocortisone were administered by four-hour intravenous infusions. Eosinophil counts were performed immediately and at four hours. No hormonal therapy other than desoxycorticosterone acetate was administered during these studies.

to be approximately twice that of cortisone. Measurements of other metabolic indexes also reveal a greater activity of hydrocortisone.[431]

A particularly striking example of the difference in potency between the two hormones is the superiority of hydrocortisone after local administration in the skin,[432] eye[421] and joints.[433] It has been suggested from these findings that cortisone, to be therapeutically effective, must be transformed to hydrocortisone, or that locally applied hydrocortisone is converted more efficiently than cortisone to a hypothetical active metabolite.[434] However, the effectiveness of cortisone after local instillation

into the conjunctival sac argues against this hypothesis. Hollander[281] has suggested that since hydrocortisone is only one seventh as soluble as cortisone in body fluids, it might diffuse less rapidly from the site of local action. The final explanation of the difference in local effectiveness between the two hormones is not known.

The marked influence observed by Conn et al.[435] of the route of administration on the metabolic actions of hydrocortisone acetate has important therapeutic implications. Hydrocortisone acetate was found to have metabolic effects of the same intensity after oral administration as free hydrocortisone given either orally or by intramuscular injection. Intramuscularly administered hydrocortisone acetate, however, was relatively inert. Salassa and his associates[436] attributed this difference to a slow rate of absorption of the acetate ester from the intramuscular depot. Boland[437] has confirmed these observations in a study of the antirheumatic effects of hydrocortisone acetate. It was believed, in addition, that the acetate ester was considerably less active than free hydrocortisone when given by mouth.

The metabolic effects of hydrocortisone in man have been demonstrated to be qualitatively similar to those of cortisone.[90, 438-440] These include a decreased carbohydrate tolerance, with glycosuria; an increased excretion of total nitrogen and uric acid; retention of sodium, chloride and water; potassium loss; and an increased excretion of calcium and phosphorus.

Hydrocortisone acetate has been shown to be capable of correcting the abnormal response of patients with Addison's disease to ingested water loads.[161] Wilkins et al.[81] and Jailer, Louchart and Cahill[441] have found intramuscularly injected hydrocortisone to be an effective inhibitor of the pituitary-adrenal system in patients with the adrenogenital syndrome. Relman and Schwartz[442] demonstrated a depression of I^{131} uptake by the thyroid gland of patients treated with orally administered hydrocortisone acetate. Clark, Blais and Tonning[443] commented on the fact that the administration of hydrocortisone to patients with rheumatoid arthritis in doses capable of giving marked metabolic effects, was accompanied by considerably less euphoria than that experienced with equal doses of cortisone. This observation corresponds with the demonstration by Woodbury[146] of a smaller decrease in the electroshock threshold of rats after hydrocortisone acetate. This difference between the two hormones has been employed to good advantage in this clinic in the treatment of patients with Addison's disease in whom average maintenance doses of cortisone induced excessive nervous stimulation. Hydrocortisone has proved effective in the dissolution of lymphoid tissue in patients with a variety of lymphomatous tumors.[148]

An increasing number of reports indicate that hydrocortisone is an effective agent for the suppression of acute inflammatory phenomena[346, 444-448] and of certain hypersensitivity phenomena.[449, 450] It is probable, therefore, that the actions of the hormone on both cellular and humoral mechanisms of defense are also similar to those of cortisone.

In summary, the over-all physiologic actions of hydrocortisone appear to be qualitatively comparable to those of cortisone, although quantitatively its effects are more intense. Whether the differences in local effectiveness between the two hormones reflect a fundamental difference in metabolism remains to be determined. Finally, the state of esterification exerts a greater influence on the rate of absorption, and therefore on the intensity of metabolic and therapeutic action, of hydrocortisone.

Toxicity

Experience to date has shown that the toxic effects of hydrocortisone are qualitatively similar to those of cortisone. Boland,[451] however, has reported that during the maintenance treatment of patients with rheumatoid arthritis fewer adverse effects are observed with free hydrocortisone than with cortisone. He attributes this difference to the fact that smaller doses of hydrocortisone are required to control the disease. A greater antirheumatic activity of free hydrocortisone does not appear to be accompanied by a corresponding increase in tendency to produce toxic complications.

Absorption, Intermediary Metabolism and Excretion

Absorption

Numerous observations that the oral administration of hydrocortisone, as either the acetate or the free alcohol, leads to striking alterations in carbohydrate, protein and electrolyte metabolism indicate that the hormone is effectively absorbed from the gastrointestinal tract. This is further illustrated by the studies of Nelson et al.[385] on the levels of plasma 17-hydroxy-corticosteroids after oral administration. These workers reported that the oral administration of hydrocortisone, as either the acetate or the free alcohol, led to a prompt rise in plasma 17-hydroxy-corticoids, with a peak at approximately one hour and a gradual return to control levels in four to eight hours. On the other hand, when hydrocortisone acetate was administered intramuscularly as a suspension in physiologic saline solution, only slight metabolic effects were observed, and no appreciable rise in the level of plasma 17-hydroxy-corticoids occurred.

Intermediary Metabolism

There is strong evidence that hydrocortisone is the principal hormone secreted by the adrenal cortex. This compound has been shown to be the chief

corticoid in dialysates of the peripheral blood of dogs,[392] in the adrenal venous blood of dogs who have been given ACTH[391, 394] and in the perfusates of bovine adrenal glands.[4] Moreover, the addition of ACTH to the perfusing fluid of bovine adrenal glands increased the output of hydrocortisone from the isolated gland.

The biosynthesis of hydrocortisone from acetate has been demonstrated in hog adrenal slices incubated with C^{14} acetate[387] and in beef adrenal glands through which radioactive acetate has been perfused.[4] Cholesterol, however, was found to be considerably more effective than acetate as a precursor.[4] From analysis of the isotopic data it was reasoned that synthesis of hydrocortisone from acetate and from cholesterol may proceed along separate pathways. Some inkling of the intermediate steps involved has come from the finding that the perfusion of progesterone through beef adrenal glands leads to an increased formation of hydrocortisone and the observation that 17-hydroxy-11-desoxy-corticosterone (Compound S) may serve as a precursor for hydrocortisone in the isolated adrenal gland[4] and in adrenal homogenates.[452]

Schneider and Horstmann[401] have presented evidence that hydrocortisone, like cortisone, is rapidly metabolized in the liver. Incubation of the hormone with rat liver slices and examination of the reaction products with the aid of ultraviolet spectroscopy, paper chromatography and the Porter–Silber and periodate oxidation assays indicated that rapid reduction of the alpha, beta unsaturated ketonic grouping in ring A and extensive degradation of the side chain at carbon-17 occurred. Similar findings were obtained when hydrocortisone was perfused through the isolated rat liver.[398]

Excretion

The administration of hydrocortisone to patients with adrenal insufficiency, like cortisone, leads to an increase in the urine of 17-ketosteroids and steroids with an alpha-ketol side chain at carbon-17. Similar findings are observed in subjects with intact adrenal glands provided the dose of hydrocortisone is sufficiently high; with small doses a fall in urinary 17-ketosteroid levels may occur. As with cortisone, the administration of hydrocortisone to patients who have undergone bilateral orchidectomy and bilateral complete adrenalectomy for metastatic carcinoma of the prostate has been found to lead to a rise in urinary biologic androgen excretion.[412] In these patients hydrocortisone has been observed to be a more effective precursor of both 17-ketosteroids (Fig. 23) and androgens than cortisone, although even at a dose of 300 mg. a day the level of urinary androgens does not exceed that of a normal man.

Hydrocortisone has been isolated from normal urine[390, 413] and from the urine of patients with Addison's disease[414, 415] and normal human subjects who have been given cortisone.[411] These findings and the recent observation that the administration of hydrocortisone to human subjects led to an increased excretion of cortisone in the urine[453] provide strong evidence that the reversible reaction, hydrocortisone ⟷ cortisone, may occur in vivo. Although no detailed investigations of specific steroids in the urine of human subjects who have received hydrocortisone have been reported, it may be inferred from studies of the steroids of normal urine and from studies of degradation in vitro[401] that the metabolism of hydrocortisone is similar to that of cortisone. The hormone may be excreted unchanged; reduction of the alpha, beta unsaturated ketone grouping in ring A may occur with the formation of tetrahydrocortisone and the tetrahydro-hydrocortisone; and finally there may be degradation of the side chain at carbon-17, with the production of 11-oxygenated 17-ketosteroids.

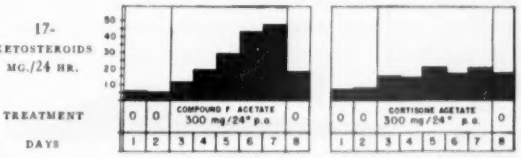

FIGURE 23. *Effect of Hydrocortisone Acetate and Cortisone Acetate on the 17-Ketosteroid Excretion after Bilateral Adrenalectomy and Bilateral Orchiectomy in a Fifty-Two-Year-Old Man with Carcinoma of the Prostate.*

PREPARATIONS AND ROUTES OF ADMINISTRATION

Hydrocortisone is presently available in the form of the acetate ester. Two preparations may be obtained: tablets for oral administration containing 20 mg. of hydrocortisone acetate; and a microcrystalline suspension in physiologic saline solution containing 0.9 per cent benzyl alcohol as preservative, and small quantities of polyoxyethylene sorbitan mono-oleate and sodium carboxy methylcellulose as suspending agents.

Orally administered hydrocortisone acetate is adequately absorbed from the gastrointestinal tract, in a manner comparable to cortisone acetate. That hydrocortisone acetate is considerably more effective after oral administration than after intramuscular injection has been emphasized above. The time-response curve of the oral preparation is quite comparable to that of cortisone acetate and, in fact, approaches that obtained by a single intravenous injection of hydrocortisone.

The saline suspension of hydrocortisone acetate is specifically dispensed for intra-articular injection in the treatment of localized, noninfectious inflammatory joint disease. The indications for its use in rheumatoid arthritis and the proper technic of in-

jection have been well outlined by Hollander[231] and by Boland.[437] Dosages range between 10 and 50 mg., depending on the size of the joint and the severity of the inflammatory process. The duration of clinical improvement after injection is variable, but ordinarily is from three to twenty-one days. That the beneficial effects produced by hydrocortisone after local injection are nonspecific is indicated by its effectiveness in osteoarthritis, traumatic arthritis, gouty arthritis, acute bursitis and the acute pleuritis of lupus erythematosus.[231]

The local administration of hydrocortisone acetate has also proved effective in disorders of the anterior segment of the eye[454] and in certain inflammatory lesions of the skin.[422] For instillation into the conjunctival sac, a collyrium may be prepared by dilution of 1 volume of the commercial suspension of hydrocortisone acetate (25 mg. per cubic centimeter) with 4 volumes of either physiologic saline solution or a 1:5000 solution of aqueous Zephiran Chloride.[454] The usual dosage schedule consists of one or two drops of the dilute suspension at hourly intervals during the day and every two to four hours at night. Experience to date indicates that hydrocortisone is somewhat more effective than cortisone in the treatment of ocular inflammatory disease.[421] Goldman[455] has demonstrated, in several ingenious experiments, a much greater suppression of cutaneous inflammation by intracutaneously injected hydrocortisone than by cortisone. Subsequently, Sulzberger and Witten,[456] using an ointment containing 25 mg. of hydrocortisone acetate per gram of base consisting of lanolin and petrolatum, observed definite improvement in the lesions of some patients with atopic dermatitis, although no response was obtained in cases of chronic discoid lupus erythematosus or chronic lichenoid dermatoses.

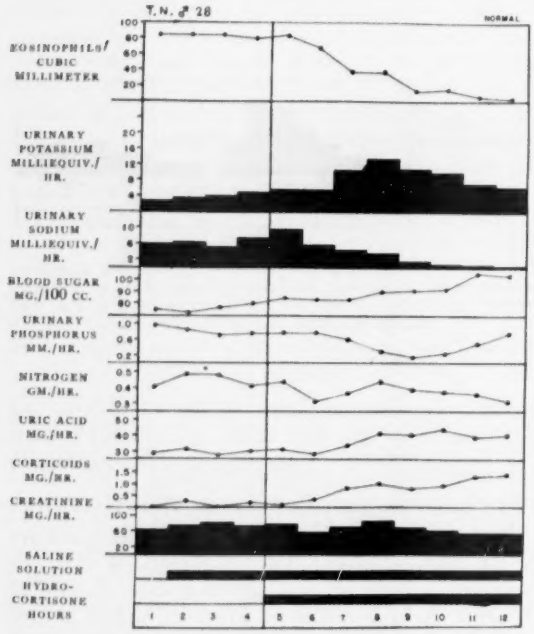

FIGURE 24. *Changes Obtained in a Normal Subject with the Intravenous Administration of Hydrocortisone (12 Mg. per Hour). The subject was in the fasting state throughout the experiment. All urinary analyses were performed on hourly specimens on one-hour collections. (Saline solution was infused at a rate of 60 cc. per hour.)*

Administration of the saline suspension of hydrocortisone acetate by intramuscular injection is not recommended for therapeutic use because of its slow absorption rate, which results in a considerable reduction in metabolic and therapeutic activity.

Solutions of hydrocortisone for intravenous use have been prepared in this laboratory[416] in the following manner: a sterile suspension of free hydrocortisone (*free alcohol*) in physiologic saline solution, containing 25 mg. per cubic centimeter, is added to sterile 95 per cent ethyl alcohol and sterile water in the order given, in the proportions of 4 cc. of steroid suspension, 5 cc. of alcohol and 3 cc. of water. The resulting clear solution is immediately diluted as desired in physiologic saline or dextrose solution for intravenous administration. When concentrations of hydrocortisone not exceeding 20 mg. per 100 cc. are required, the saline suspension of hydrocortisone may be dissolved directly in either the saline or the dextrose diluent. The majority of metabolic and therapeutic studies on the intravenous administration of adrenocortical hormones have employed hydrocortisone, and a satisfactory preparation will soon be available for clinical use.

In situations in which a rapid and intense hormone effect is necessary, the intravenous infusion of hydrocortisone is the procedure of choice since the chief advantage offered by this route is the rapidity with which metabolic effects of *maximal* intensity are produced. Figure 24 shows the changes elicited in a fasting normal subject by the intravenous administration of hydrocortisone at a rate of 12 mg. per hour. A satisfactory eosinopenia and uricosuresis were obtained. Particularly striking were the rapid and impressive changes in urinary electrolyte excretion: a pronounced rise in potassium output and an almost complete suppression of sodium excretion. The absence of an increase in total urinary nitrogen indicates that, during the initial acute phase of hormone action, the elevation of blood sugar cannot be adequately accounted for by an augmented gluconeogenesis from protein. The progressive rise in total 17-hydroxycorticoid excretion establishes the time-response curve of urinary corticoid excretion in the presence of a sustained high level of circulating hydrocortisone. In view of the intensity of hormonal effects on both organic and inorganic metabolism, intravenous hydrocortisone therapy is

clearly indicated in existing or potential states of acute adrenocortical insufficiency.

In summary, if the pharmacologic triad of increased potency, without proportionate increase in toxicity, and an increased effectiveness when administered locally in the joint and the eye is borne out by future clinical experience, it appears possible that hydrocortisone will become the adrenal corticoid of choice in the therapy of diseases in which 11,17-oxysteroids are of value.

ADRENOCORTICAL EXTRACTS

After the description by Addison[457] of a clinical syndrome associated with destruction of the adrenal glands, and the subsequent demonstration by Brown-Séquard[458] of the inability of animals to survive bilateral adrenalectomy, sporadic attempts were made to prepare whole adrenal extracts for clinical use. One of the earliest attempts in this direction was the study made by Osler,[382] who described in 1896 the use of an adrenal extract that he had prepared from fresh adrenal glands (hog), kept in the cold and extracted with glycerin. It was not until many years later that it was fully appreciated that adrenal glands must be fresh and that preservation in the cold was essential for good yield; that glycerin was one of the most effective solvents — especially for orally administered extracts; and that hog adrenal glands possessed a particularly high concentration of 11-17-oxysteroids. It was not realized in these earlier studies that only the cortex of the gland contained the life-maintaining principle. Hence, it came as a keen disappointment that the isolation of epinephrine failed to provide a hormone that would increase the survival of adrenalectomized animals. Attention was therefore turned to the isolation of the active principle from the cortex of the gland.

In 1927 Hartman, MacArthur and Hartman[459] and Rogoff and Stewart[460] independently reported the preparation of adrenocortical extracts that were capable, on injection, of prolonging the survival of adrenalectomized animals. Three years later Swingle and Pfiffner[461] and Hartman and Brownell[462] described methods of preparing adrenocortical extracts of much greater potency. Bilaterally adrenalectomized dogs and cats were maintained in good condition for prolonged periods with these extracts, and patients with Addison's disease were greatly improved. Later refinements included the preparation by Kuizenga et al.[463] of a highly purified extract (lipoadrenal extract) that was standardized on the basis of its content of 11- and 17-oxysteroids.

Adrenocortical extracts possess all the physiologic properties known to be mediated by the secretion of the adrenal cortex. "Electrolyte-regulating" effect was demonstrated in normal subjects as well as in patients with Addison's disease.[461] "Carbohydrate-regulating" capacity of adrenal extracts was shown in conjunction with the maintenance of patients with Addison's disease and in the treatment of acute adrenal crisis.[465] After long-continued therapy with adrenal extract, a diminution in Addisonian pigmentation has been reported.[466] From metabolic studies it appears that 3 to 6 cc. of the purified lipoadrenal cortex is equivalent in its effect on sodium, chloride and nitrogen excretion to that of 15 to 30 mg. of dehydrocorticosterone.[83]

Side reactions after administration of highly purified adrenal extracts are almost unknown. Occasionally, in conjunction with supplementary sodium chloride therapy, edema occurs. The rapid administration of "aqueous" adrenal extract intravenously may give rise to tachycardia, palpitation and tremor in patients known to be sensitive to the action of epinephrine.

So-called "aqueous" extracts of adrenal cortex are rapidly absorbed after subcutaneous and intramuscular injection. The duration of action after a single injection ranges from one to four hours. This type of extract may also be given intravenously, with instantaneous effect. The lipoadrenal extract for intramuscular use is more slowly absorbed, and hence a more prolonged effect from a single injection may be anticipated. Relatively large quantities of extract must be given by mouth to elicit a demonstrable physiologic effect.[467]

The high cost of preparing potent adrenocortical extracts, and the limited total source of supply, preclude their widespread clinical use. During the period 1930–1950, adrenocortical extracts were employed principally in the treatment of acute adrenal crisis.

As the synthesis of additional steroids was accomplished, the properties of the new compounds were compared with those of standardized extracts. The electrolyte-regulating capacity of adrenal extracts and crystalline steroids were measured by classic renal-excretion studies.[468] However, after the synthesis of desoxycorticosterone primary interest centered on the possible "carbohydrate-regulating" potency of new compounds. Hence, tests other than electrolyte regulation and maintenance of growth were required. Great credit must be given Ingle[94] for his meticulous standardization of a work-performance test in rats. This biologic assay method proved exceedingly accurate in evaluation of the "carbohydrate-regulating" efficacy of adrenocortical extracts and crystalline adrenal-steroid substances.

At present the clinical use of adrenocortical extracts has decreased appreciably in view of the relatively low cost of synthetic 11-desoxycorticosterone, cortisone and hydrocortisone. It is a matter of more than academic interest, however, that to date no combination of steroids, assayed by the Ingle technic, has proved superior in effectiveness to adrenocortical extract. There appear to be still unidentified factors in the amorphous fraction of adrenal-gland extracts whose activity

exceeds that of desoxycorticosterone, corticosterone and hydrocortisone.

Two types of adrenocortical extracts are available commercially for clinical use: extracts derived from beef adrenal glands in aqueous solution suitable for subcutaneous, intramuscular or intravenous use; and a single, highly purified extract, derived from hog adrenal glands, prepared in sesame oil for intramuscular use only and assayed in terms of its corticosterone and cortisone equivalence.

For the daily maintenance therapy of patients with Addison's disease adrenal extracts have been replaced almost entirely by a combination of desoxycorticosterone acetate and cortisone or hydrocortisone. Aqueous adrenal extract has a useful place in the therapeutic armamentarium of acute adrenal crisis, particularly in the absence of a commercially available preparation of cortisone or hydrocortisone for intravenous use. In the treatment of adrenal crisis or acute adrenal insufficiency, adrenocortical extracts may be used as follows: 30 to 50 cc. of aqueous adrenal extract injected rapidly as an intravenous infusion followed by 10 cc. of aqueous adrenal extract or 2 cc. of lipoadrenal extract intramuscularly every one or two hours for twelve hours and then every two to three hours for the next twelve-hour period: this is followed by 5 to 10 cc. of aqueous adrenal extract or 1 to 2 cc. of lipoadrenal extract. Subsequently, the dose is maintained, but the period of administration is increased to intervals of three, four and six hours.[48]

Whether or not adrenal extracts possess any distinct value in the maintenance therapy of Addison's disease over and above that of cortisone and hydrocortisone supplemented with desoxycorticosterone is not known. Certainly the over-all difference cannot be great, since cortisone and hydrocortisone have been used repeatedly with great success as the sole source of adrenal-hormone therapy in the treatment of adrenal crisis.

(*To be continued in a later issue*)

References

416. Garcia-Reyes, J. A., McCracken, B. H., Thorn, G. W., and Jenkins, D. Unpublished data.
417. Thorn, G. W., Jenkins, D., McCracken, B. H., Garcia-Reyes, J. A., and Reddy, W. J. Recent studies on ACTH and cortisone. *Tr. A. Am. Physicians* **65**:281-292, 1952.
418. Henderson, E., Gray, J. W., Weinberg, M., and Merrick, E. Z. Subcutaneous implantation of cortisone pellets in rheumatoid arthritis. *Science* **114**:243, 1951.
419. Steffanson, E. H. Corticotropin, cortisone and hydrocortisone in treatment of ocular disease. *J. A. M. A.* **150**:1660-1664, 1952.
420. Leopold, I. H., Purnell, J. E., Cannon, E. J., Steinmetz, C. G., and McDonald, P. R. Local and systemic cortisone in ocular disease. *Am. J. Ophth.* **34**:361-371, 1951.
421. Smith, R. W., Jr., and Steffensen, E. H. ACTH and cortisone in treatment of ocular disease. *New Eng. J. Med.* **245**:972-978 and 1007-1013, 1951.
422. Koff, R., et al. Subconjunctival injection of cortisone in iritis. *J. A. M. A.* **144**:1259, 1950.
423. Gelfand, M. L. Administration of cortisone by aerosol method in treatment of bronchial asthma. *New Eng. J. Med.* **245**:293, 1951.
424. Newman, B. A., and Feldman, F. F. Effects of topical cortisone on chronic discoid lupus erythematosus and necrobiosis lipoidica diabeticum. *J. Invest. Dermat.* **17**:3-6, 1951.
425. Mason, H. L., Hoehn, W. M., and Kendall, E. C. Chemical studies of suprarenal cortex: structures of compounds C, D, E, F and G. *J. Biol. Chem.* **124**:459-474, 1938.
426. Ingle, D. J. Work performance of adrenalectomized rats treated with corticosterone and chemically related compounds. *Endocrinology* **26**:472-477, 1940.
427. Olson, R. E., Thayer, S. A., and Kopp, L. J. Glycogenic activity of certain crystalline steroids of adrenal cortex when administered singly and with cortical extract to fasted, normal and adrenalectomized rats. *Endocrinology* **35**:464-472, 1944.
428. Mason, H. L., and Sprague, R. G. Isolation of 17-hydroxycorticosterone from urine in case of Cushing's syndrome associated with severe diabetes mellitus. *J. Biol. Chem.* **175**:451-456, 1948.
429. Wendler, N. L., Graber, R. P., Jones, R. E., and Tishler, M. Synthesis of 11-hydroxylated cortical steroids. 17 (α)-hydroxycorticosterone. *J. Am. Chem. Soc.* **72**:5793, 1950.
430. Ingle, D. J., Nezamis, J. E., and Morley, E. H. Work performance of adrenalectomized rats given cortisone and 17-hydroxycorticosterone by continuous intravenous injection. *Proc. Soc. Exper. Biol. & Med.* **78**:79-81, 1951.
431. Conn, J. W. Discussion of Sprague, R. G. Clinical use of adrenal cortical hormones and ACTH. In *Transactions of the Third Conference on the Adrenal Cortex*. 204 pp. Edited by E. P. Ralli. New York: Josiah Macy Jr., Foundation, 1952. P. 187.
432. Goldman, L., and Baskett, J. Compound F in dermatology. Presented at the Academy of Dermatology and Syphilology of the College of Medicine of the University of Cincinnati, Chicago, December, 1952.
433. Hollander, J. L. Local effects of Compound F (hydrocortisone) injected into joints. *Bull. Rheumat. Dis.* **2**:3, 1951.
434. Pincus, G. Some basic hormone problems. *J. Clin. Endocrinol. & Metab.* **12**:1187-1196, 1952.
435. Conn, J. W., et al. Metabolic effects in man of orally and parenterally administered compound F (17-hydroxycorticosterone) and compound F acetate. *J. Lab. & Clin. Med.* **38**:799, 1951.
436. Salassa, R. M., Power, M. H., Mason, H. L., and Sprague, R. G. Comparative metabolic effects of intramuscular use of cortisone acetate and 17-hydroxycorticosterone (Compound F) acetate. *J. Clin. Investigation* **31**:658, 1952.
437. Boland, E. W. Rheumatoid arthritis: experiences with hydrocortisone (free alcohol) and hydrocortisone acetate. *California Med.* **77**: 1-6, 1952.
438. Fourman, P., et al. Effects of 17-hydroxycorticosterone ("compound F") in man. *J. Clin. Investigation* **29**:1462-1473, 1950.
439. Perera, G. A., Ragan, C., and Werner, S. C. Clinical and metabolic study of 17-hydroxycorticosterone (Kendall compound F): comparison with cortisone. *Proc. Soc. Exper. Biol. & Med.* **77**:326-330, 1951.
440. Conn, J. W., Louis, L. H., and Fajans, S. S. Probability that Compound F (17-hydroxycorticosterone) is hormone produced by normal human adrenal cortex. *Science* **113**:713, 1951.
441. Jailer, J. W., Louchart, J., and Cahill, G. F. Adrenal virilism. II. Metabolic studies. *J. Clin. Investigation* **31**:880-884, 1952.
442. Relman, A. S., and Schwartz, W. B. Metabolic effects of Compound F acetate in man. *J. Clin. Investigation* **31**:656, 1952.
443. Clark, W. S., Blais, J. A., and Tonning, H. O. Antirheumatic and metabolic effects of hydrocortisone in rheumatoid arthritis. *J. Clin. Investigation* **31**:621, 1952.
444. Goldman, L., Rockwell, E., and Richfield, D. F. III. Histopathological studies on cutaneous reactions to bites of various arthropods. *Am. J. Trop. Med. & Hyg.* **1**:514-525, 1952.
445. Woods, A. C., and Wood, R. M. Studies in experimental ocular tuberculosis. XVI. Effect of corticotropin, cortisone, and compound F on development of experimental ocular tuberculosis in immune-allergic and normal rabbit. *Arch. Ophth.* **47**:477-512, 1952.
446. Stevenson, C. R., Zuckner, J., and Freyberg, R. H. Intra-articular hydrocortisone (Compound F) acetate: preliminary report. *Ann. Rheumat. Dis.* **11**:112-118, 1952.
447. Kersley, G. D., and Desmarais, M. H. L. Intra-articular hydrocortisone acetate in rheumatoid arthritis. *Lancet* **2**:269, 1952.
448. Boland, E. W. Clinical use of cortisone, hydrocortisone, and corticotropin. *J. A. M. A.* **150**:1281-1288, 1952.
449. Goldman, L., Preston, R. H., Rockwell, E., and Baskett, J. Inhibition of tuberculin reaction by local injection of compound F. *J. A. M. A.* **150**:30, 1952.
450. Rosenthal, M. C., Spaet, T. H., Goldenberg, H., and Dameshek, W. Treatment of acquired haemolytic anaemia with compound F acetate. *Lancet* **1**:1135-1140, 1952.
451. Boland, E. W., and Headley, N. E. Compound F used orally in patients with rheumatoid arthritis. *J. A. M. A.* **148**:981-987, 1952.
452. McGinty, D. A., Smith, G. N., Wilson, M. L., and Worrel, C. S. Biosynthesis of 17-hydroxycorticosterone from 11-desoxy-17-hydroxycorticosterone. *Science* **112**:506, 1950.
453. Burstein, S., Savard, K., and Dorfman, R. I. Unpublished data.
454. Steffensen, E. H., Ivy, H. B., and Nagle, F. O. Topical compound F in treatment of anterior segment eye disease: preliminary report. *Am. J. Ophth.* **35**:933, 1952.
455. Goldman, L. Local effect of compound F on reactions to mosquito bites. *J. A. M. A.* **149**:265, 1952.
456. Sulzberger, M. B., and Witten, V. H. Effect of topically applied compound F in selected dermatoses. *J. Invest. Dermat.* **19**:101, 1952.
457. Addison, T. On constitutional and local effects of disease of suprarenal capsules. London: D. Highley, 1855.
458. Brown-Séquard, E. Recherches expérimentales sur la physiologie et la pathologie des capsules surrénales. *Arch. gén. de méd.* **8**:385-401, 1856.
459. Hartman, F. A., MacArthur, C. G., and Hartman, W. E. Substance which prolongs life of adrenalectomized cats. *Proc. Soc. Exper. Biol. & Med.* **25**:69, 1927.
460. Rogoff, J. M., and Stewart, G. N. Influence of adrenal extracts on survival period of adrenalectomized dogs. *Science* **66**:327, 1927.

461. Swingle, W. W., and Pfiffner, J. J. Aqueous extract of suprarenal cortex which maintains life of bilaterally adrenalectomized cats. *Science* **71**:321, 1930.

462. Hartman, F. A., and Brownell, K. A. Hormone of adrenal cortex. *Proc. Soc. Exper. Biol. & Med.* **27**:938, 1930.

463. Kuizenga, M. H., Wick, A. N., Ingle, D. J., and Nelson, J. W. Preparation and comparative physiologic activities of beef, hog and sheep adrenal cortex extracts. *J. Biol. Chem.* **147**:561-565, 1943.

464. Thorn, G. W., Garbutt, H. R., Hitchcock, F. A., and Hartman, F. A. Effect of cortin upon renal excretion of sodium, potassium, chloride, inorganic phosphorus and total nitrogen in normal subjects and in patients with Addison's disease. *Endocrinology* **21**: 213-219, 1937.

465. Hartman, F. A., Thorn, G. W., Lockie, L. M., Greene, C. W., and Bowen, B. D. Treatment of Addison's disease with extract of suprarenal cortex (cortin). *J. A. M. A.* **98**:788-793, 1932.

466. Hartman, F. A., Greene, C. W., Bowen, B. D., and Thorn, G. W. Further experience with cortin therapy. *J. A. M. A.* **99**:1478-1482, 1932.

467. Thorn, G. W., Emerson, K., Jr., and Eisenberg, H. Oral therapy in adrenal insufficiency. Efficacy of concentrated adrenal cortical extract preserved in glycerol. *Endocrinology* **23**:403-418, 1938.

468. Thorn, G. W., Engel, L. L., and Eisenberg, H. Effect of corticosterone and related compounds on renal excretion of electrolytes. *J. Exper. Med.* **68**:161-171, 1938.

MEDICAL INTELLIGENCE

THE IDENTIFICATION OF PENTOBARBITAL BY PAPER CHROMATOGRAPHY IN A MEDICOLEGAL DEATH*

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THE results of an investigation of the application of paper chromatography to the identification of the common barbiturates were recently reported by this laboratory.[1]

If a barbiturate is found to be responsible for a medicolegal death, the investigator is compelled to engage in as complete and detailed a study as biologic material available allows so that the results can be fully evaluated and the drug identified. Important factors in the final appraisal are the metabolic fate and distribution of the barbiturates in the human body.

It is here that the advantages of paper chromatography may be realized, for this simple technic may yield information regarding the presence of unchanged drug as well as its metabolites in body fluids and organs, and only extremely small amounts are necessary for this accomplishment.

Elaboration of details in the following case, which involved a medicolegal death by pentobarbital, the identity of the barbiturate being established by paper chromatography, demonstrates the potentials of this technic:

The death of a wealthy man was attributed to heart failure by the attending physician. The family of the deceased questioned the verdict, believing that he had taken his own life, and requested that an autopsy be performed to determine the actual cause of death. The proper settlement of the estate and testating of the will, which had been changed before death to exclude the immediate family, depended upon a complete investigation of the circumstances of his death. Important, too, was the information that he had at one time been under psychiatric treatment.

As a result of the autopsy, death from natural causes was ruled out, and the problem became one for the chemist.

Specimens submitted for analysis consisted of urine, gastric contents and blood; 5 cc. of blood was analyzed according to the ultraviolet spectrophotometric method of Walker, Fisher and McHugh.[2] Barbiturate was found in a concentration of 4.2 mg. per 100 cc. of blood (calculated, like all other levels given in this report, on the basis of pentobarbital).

Extraction of 2 cc. of the urine (pH 5.2) was accomplished by shaking in a separatory funnel with two 25-cc. portions of ether. The procedure was then continued as for blood after the solvent extracts had been combined. The concentration of barbiturate in the urine was 72 mg. per 100 cc.

A 10-gm. portion of stomach contents was suspended in 100 cc. of water acidified with sulfuric acid, shaken and filtered. A 10-cc. aliquot of the filtrate was extracted three times with equal volumes of chloroform. The procedure was continued as for blood after combination of the solvent extracts. The entire gastric contents were found to contain 2.2 gm. of barbiturate.

After determination of the concentrations reported above, multiple applications of appropriate amounts of barbiturate were made on filter paper prepared for ascending chromatography. Complete details of this manipulation, preparation of the solvent mixture and subsequent treatment of the paper upon completion of development to locate the positions of material containing the barbiturate ring are reported elsewhere.[1]

The procedure outlined was followed, but in cases such as this it has been the routine practice to divide the sheet into two vertical strips. The chemical tests were applied to one strip. The other strip was cut into equal segments. Each section was eluted with 0.05 normal solution of sodium hydroxide. The spectrums of this solution were obtained at pH 10 and 2. This treatment reveals the presence of the barbituric acid ring.[2,3] The process of elution and of spectral determination was necessary since it has been found that the color tests may not be completely reliable for the location of zones when metabolic products and uncertain amounts are involved. The elution serves as a complete check of all the constituents present.

On the chromatogram of the extracts of the stomach contents and blood, barbiturate was found to be concentrated at R_f 0.73 — the position normally occupied by pentobarbital.

However, the chromatogram of the urine extract revealed barbiturate at three distinct zones — at R_f 0.08, 0.46, and 0.73. On this sheet, 360γ of the barbiturate from 0.5 cc. of urine had been resolved. The recoveries of barbiturate after elution with sodium hydroxide of the entire sheet were: 160γ at R_f 0.46, 120γ at 0.08, and 10γ at 0.73.

This chromatographic pattern of the urinary constituents extracted under the stated conditions was recognized as being exactly the same as that of urinary extracts obtained in the same way after administration of pentobarbital to dogs and human beings in experimental studies conducted by this laboratory. Those studies provided a valid basis for the comparison here and also established the location on the chromatogram of two urinary metabolites of pentobarbital. These two end-products were isolated from dog urine and characterized as being the diastereoisomers of 5-ethyl-5-(3-hydroxy-1-methylbutyl) barbituric acid by Maynert and his co-workers.[4-6] The location of these metabolites at R_f 0.46 was verified by actual isolation and characterization of these materials from chromatograms of dog urine extracts.

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In the same studies we have consistently noted the presence of still a third, unclassified metabolite, which is located at R_f 0.08 on chromatograms of both dog and human urine extracts. This substance possesses the barbituric acid ring, and gives indication of being a carboxylic acid. So far it has resisted all attempts at purification. The results of the experimental studies referred to above are being reported in detail elsewhere.

The logical consequence in the case under discussion was to confirm the conclusions derived from the chromatographic patterns by actual isolation of metabolites from the urine available and also of unchanged drug from the gastric contents.

A portion of the gastric contents was treated in the customary manner to isolate the pure barbiturate ingested. After recrystallization from water of the crystalline solid that resulted after extraction, the extinction coefficient, melting point and mixed melting point with pure pentobarbital proved that the material was pentobarbital.

As previously stated it was found that 0.5 cc. of urine contained 160γ of the barbiturate concentrated at R_f 0.46. Therefore, the total urine sample (430 cc.) should yield 140 mg. of the two diastereoisomers at R_f 0.46. At this time we have not been able to separate and characterize the small amount of material obtained from this zone. There is good but not entirely conclusive evidence that the two diastereoisomers are present.

References

1. Algeri, E. J., and Walker, J. T. Paper chromatography for identification of common barbiturates. *Am. J. Clin. Path.* **22**:37-40, 1952.
2. Walker, J. T., Fisher, R. S., and McHugh, J. J. Quantitative estimation of barbiturates in blood by ultra-violet spectrophotometry. I. Analytical method. *Am. J. Clin. Path.* **18**:451-461, 1948.
3. Goldbaum, L. R. Determination of barbiturates: ultraviolet spectrophotometric method with differentiation of several barbiturates. *Anal. Chem.* **24**:1604-1607, 1952.
4. Maynert, E. W., and van Dyke, H. B. Isolation of metabolite of pentobarbital. *Science* **110**:661, 1949.
5. Maynert, E. W., and Dawson, J. M. Ethyl (3-hydroxy-1-methylbutyl) barbituric acids as metabolites of pentobarbital. *J. Biol. Chem.* **195**:389-395, 1952.
6. Maynert, E. W. Distribution and fate of dialkylbarbiturates. *Federation Proc.* **11**:625-631, 1952.

DOCTORS AFIELD

Samuel Gridley Howe

Peter Pineo Chase, M.D.*

PROVIDENCE, RHODE ISLAND

RARELY, if ever, has any Boston doctor been farther afield than Samuel Gridley Howe. This is not to speak, of course, in great circle miles, but the mountains of Greece in 1825 were far away in time and circumstance.

He was born on Pearl Street, probably, then, just on the outskirts of the best neighborhood in Boston. He went to the Boston Latin School, and since the family could afford to send only one boy to college, Sam was picked. The test was the reading of the Bible. Politics were taken seriously around Boston in those days. Harvard was Federalist, so he was sent to Brown University in Providence, Rhode Island. Here he formed a lasting friendship with Horace Mann and equipped himself with a sound knowledge of Latin and a thorough one of English and with a passion for history and poetry.

These influenced his life more than his four years at Harvard Medical School. It is said that he was not much of a doctor. Ophthalmology probably played little, if any, part in his life work at the Massachusetts School and Asylum for the Blind. He was an administrator, teacher and missionary.

Byron, at the beginning of the nineteenth century stirred readers of his poetry in a manner most certainly not achieved by the peculiar modern poets of the present. Young Howe was among the most enthusiastic. Laura E. Richards remembers her father in later life reciting many Byronic Greek references.

> Slow sinks, more lovely ere his race be run,
> Along Moria's hills the setting sun.

or the familiar. . .

> The Isles of Greece, the Isles of Greece
> Where burning Sappho loved and sang.

When Byron joined the Greek Revolution, Sam Howe, just through medical school, had to follow him. Byron died before Howe got there. Who did more for Greece? Possibly Byron. His verses roused Europe and America. Howe's concrete achievements far surpassed his idol's, and here is a striking example of how words rather than deeds linger in human memories: Julia Ward Howe, who wrote one famous poem, *The Battle Hymn of the Republic*, is probably known to more Americans than her husband, in spite of his great achievements.

The Turko–Greek war was no gentlemen's quarrel. Howe, dressed in his "snowy chemise and shaggy capote," carried his yataghan and pistols and "only became a surgeon when the fighting was over." He often slept on the ground, and ate sorrel and snails and "wasps roasted to a crisp and strung on a straw like roasted cherries, they were not at all bad."

It was all rough, but not all as bad as this. They might shoot a sheep, belonging of course to a fellow Greek, and on at least one occasion they also shot the shepherd. The meat they cut in chunks and toasted on their ramrods. He notes one piece of medical work not in the regular line of duty. An officer asked him to see a sick woman. He was surprised that even any old hags should be thereabouts, but in a hut he found a beautiful young girl. "Her confusion and partial undress made her the more interesting and entirely destroyed my equilibrium."

After two and a half years, with the Greeks usually on the run, the Turks were stopped, largely by

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European navies, and Howe came home. He crusaded for their cause and after a year was back in Greece with supplies which he distributed. He organized work projects, but in two years he contracted "swamp fever," which troubled him the rest of his life.

When able to travel, he went to Paris. One of the frequent French Revolutions, the one known as "the Three Days," started, and naturally he wanted to get into it. Lafayette, however, insisted that it was a private fight, so Howe returned home.

Massachusetts had recently incorporated the Asylum for the Blind, and Howe was quickly chosen to head it. He started right back to Europe to study for the job. When he prepared to go to Berlin Lafayette persuaded him to carry money and supplies to the Poles, who had recently been almost annihilated by the Prussians.

Before he had got far with this the Prussian government ordered him from the frontier, and when he arrived in Berlin he was arrested at his hotel. Fortunately, he had just given his name and address to a fellow countryman. He had time to stuff his important papers into the hollow head of a bust of the King of Prussia and tear into fine bits some trivial ones, which he threw into a basin of water. The success of the police in putting these together is one of the earliest recorded examples of a picture-puzzle solution. He was in prison five weeks and was forced on leaving to pay for his board and lodging. Years later the King of Prussia sent him a medal for his work with the blind. He weighed and analyzed it and found its value just equal to his prison bill. Ten years after Howe's imprisonment Horace Mann removed the papers from the King's calvarium.

Dr. Howe then returned to America, took several blind children into his father's home, moved from there to the home of Colonel Thomas Handasyd Perkins on Pearl Street, later to the Perkins Institution in South Boston, "had the good fortune" to discover Laura Bridgman, the blind deaf and dumb girl in Hanover, New Hampshire, and taught her to do about everything but speak, became the husband of Julia Ward Howe, worked with Dorothea Dix for the Insane and Feeble Minded, joined heartily in the Abolitionist movement, organized the State Charities of Massachusetts, made other trips to Europe, Greece and Crete, and died in his seventy-fifth year.

He was a man of tremendous action, indomitable determination and Quixotic spirit, although it was said that he could distinguish giants from windmills and that he always brought his giant down.

His associates idolized him, and yet, as Frank B. Sanborn, "Boswell of the Concord worthies," said: "I am not here to say that our hero and philanthropist was faultless." Men like him live in a black and white world. He was as Sanborn described him:

> Lofty and sour to those who loved him not,
> But to the souls that loved him, sweet as summer.

One of his former students said, "There were two laws; the doctor's and another. If we transgressed the doctor's we caught it, but we did not care much about the other one."

He did not so much as Boswell delight in "that intellectual chymistry which can separate good qualities from evil in the same person." But these defects were minor. He had an incredible record of

FIGURE 1. *Portrait of Samuel Gridley Howe, M.D. (John Hay Library, Brown University), Painted by John Elliott, his Son-in-Law.*

achievement, and it is given to few men to inspire such love. Two American poets, perhaps not of the quality of his admired Byron, nevertheless characterized him in verse. The first was Whittier:

> . . .Behold him
> The Cadmus of the blind,
> Giving the dumb lip language,
> The idiot clay a mind.

And the other was medicine's own Dr. Holmes:

> He touched the eyelids of the blind,
> And lo! the veil withdrawn,
> As o'er the midnight of the mind
> He led the light of dawn.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 39101

PRESENTATION OF CASE

First admission. A fifty-two-year-old woman was referred to this hospital for study.

The patient, who had always been extremely nervous, a month before admission while attempting to get out of bed suffered a severe pain in the posterior midthoracic region that forced her to remain in bed at home for ten days. At the end of this time she was admitted to another hospital, where it was discovered that she had a compression fracture of the fourth thoracic vertebra and generalized bony decalcification. On admission she complained of generalized aches and pains, nocturia, constipation and ankle swelling. She denied abdominal or flank pain or hematuria.

Physical examination revealed a moderately obese, anxious woman. Aside from an enlarged nodular right thyroid lobe, the examination was not remarkable.

The temperature was 98.6°F., the pulse 110, and the respirations 20. The blood pressure was 160 systolic, 100 diastolic.

The urine had a specific gravity of 1.004 and gave a ++ test for albumin; the sediment was loaded with white cells. A Sulkowitch test was ++. Examination of the blood showed a hemoglobin of 11 gm. per 100 cc. and a white-cell count of 8300, with a normal differential. The blood calcium was 15.5 mg., the phosphorus 3.8 mg., the alkaline phosphatase 21 units, the sugar 103 mg., the total protein 7.1 gm., the albumin 5.2 gm., the globulin 1.9 gm., the cholesterol 399 mg., and the nonprotein nitrogen 42 mg. per 100 cc.; the chloride was 92 milliequiv. per liter, and the prothrombin time 15 seconds (normal, 15 seconds). Twenty-four-hour urine specimens contained 214 to 240 mg. of calcium.

On the seventh hospital day an operation was performed, and a tumor of the left lower parathyroid gland, weighing 4 gm., and subsequently reported by the pathologist as carcinoma, was removed from behind the lower pole of the left lobe of of the thyroid gland. Postoperatively the Sulkowitch test of the urine became negative, and the blood calcium was 8.4 mg., the phosphorus 3.2 mg., and the alkaline phosphatase 17.6 units per 100 cc. The patient was treated with absolute bed rest and discharged on the forty-eighth hospital day with "remarkable change in personality, joking and cooperative," and though not walking yet, she was able to stand.

Second and third admissions (eight months and twenty-three months, respectively, after the first admission). In the interval the patient was much improved clinically and was able to be up and around. The second admission was for follow-up purposes. At this time examination of the blood disclosed a total protein of 7.6 gm., a nonprotein nitrogen of 58 mg., a calcium of 9.7 mg., a phosphorus of 2.4 mg., and an alkaline phosphatase of 4.8 units per 100 cc. A plain film of the abdomen showed punctate foci of calcification throughout both kidneys (Fig. 1). During the six months before the third admission the patient had felt fairly well but had noted a nodule in the region of the operative scar that had gradually increased in size. At this time the blood calcium was 13.5 mg., the phosphorus 2.5 mg., and the alkaline phosphatase 9.5 units per 100 cc. During this admission the nodule noted by the patient was removed and found to be recurrent carcinoma.

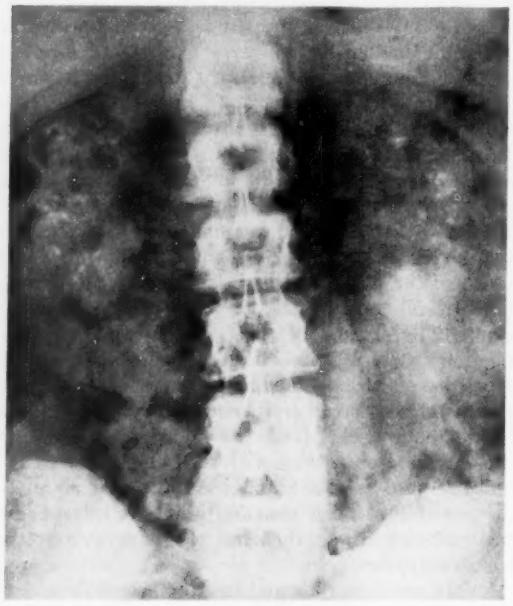

FIGURE 1.

Fourth and fifth admissions (three weeks and three and a half months, respectively, after the third

admission). The fourth admission was for observation. The blood calcium was 12.3 mg., the phosphorus 3.9 mg., and the alkaline phosphatase 5.8 units per 100 cc. Three months later the patient returned because of tingling in the left index finger for a week. Otherwise she was asymptomatic. The serum nonprotein nitrogen was 45 mg., the total protein 7.1 gm., the calcium 13.8 mg., the phosphorus 3.6 mg., and the alkaline phosphatase 14.2 units per 100 cc. A left radical neck dissection was done, and five separate tumor nodules were removed. Postoperatively, the blood calcium was 10.6 mg., the phosphorus 3.7 mg., and the alkaline phosphatase 10.3 units per 100 cc.

Sixth, seventh and eighth admissions (two months, five months and eight months, respectively, after the fifth admission). During this period the patient felt much improved clinically and was able to be up and around. She returned for follow-up studies. The findings on physical examination were unchanged. The highest urine specific gravity recorded was 1.012, and all urine specimens gave a ++ to +++ test for albumin, with many white cells and bacteria in the sediment. The following are the calcium, phosphorus and alkaline phosphatase values for the three admissions, in the order indicated: sixth admission, 11.6 mg., 3.1 mg. and 12.5 units per 100 cc.; seventh admission, 12.4 mg., 3.0 mg. and 10.4 units per 100 cc.; and eighth admission, 10.0 mg., 3.7 mg. and 14.7 units per 100 cc. The nonprotein nitrogen at the time of the eighth admission was 64 mg. per 100 cc.

Final admission (three months later, or about three years and three months after the first discharge). After discharge from the hospital the patient was treated with chloramphenicol by her physician and felt well for the first month, after which she became nauseated and had remained so ever since. She could not retain food and had "heartburn" described as pain coming up around both sides of the chest and up the sternum to the manubrial notch, deep seated and accompanied by a feeling of nausea. She could move around perfectly well, but when she sat up in a chair very long the "heartburn" came on and she vomited. Because of this she had remained in bed for much of the previous two months. During this period numbness of the right leg had reappeared, as well as some numbness and pain starting in the dorsum of the midportion of the left foot radiating upward. Moving her legs did not bring on the pain. She had lost 20 pounds of weight but had regained half of this. She was weak and dizzy when she stood up.

Physical examination did not show any new findings. The temperature was 98°F., the pulse 90, and the respirations 25. The blood pressure was 135 systolic, 85 diastolic.

Examination of the blood revealed a hemoglobin of 11.6 gm. per 100 cc. and a white-cell count of 9700. The nonprotein nitrogen was 85 mg., the total protein 7.4 gm., the calcium 14.7 mg., the phosphorus 4.7 mg., the alkaline phosphatase 7.3 units, the cholesterol 503 mg., and the cholesterol esters 322 mg. per 100 cc. A twenty-four-hour urine specimen contained 120 mg. of calcium. A stool specimen was brown and guaiac negative. A urine culture grew out abundant colon bacilli. X-ray studies, of the chest, including fluoroscopy and planigrams, were normal. A barium-swallow examination demonstrated slight deviation of the esophagus to the left in the upper portion of the neck. A roentgenogram of the spine showed collapse of the third and fourth thoracic vertebras noted earlier. There was marked generalized decalcification but no obvious progression since the previous examinations. Examination of the right leg disclosed an expansile cyst-like lesion of the lower fibula (Fig. 2) that had been noted at the time of the seventh admission and seemed slightly larger.

FIGURE 2.

On the sixteenth hospital day the right side of the neck was explored and a mass measuring 1.5

by 1.9 by 0.7 cm. and weighing 1 gm. was removed from alongside the esophagus posterior to the level of the trachea. This was subsequently reported by the pathologist as a parathyroid adenoma. On the first postoperative day expiratory stridor developed, necessitating a tracheotomy. The temperature had risen to 100.5°F., and the pulse to 140; the respirations were 20. The serum calcium was 13.3 mg., the phosphorus 6.5 mg., and the alkaline phosphatase 9.1 units per 100 cc. Twenty-four hours later the patient complained of generalized abdominal pain and tenderness. The nonprotein nitrogen was 106 mg., and the amylase 168 units per 100 cc. On the following day she did not complain of abdominal pain, but the abdomen was tender on pressure. The white-cell count was 16,800, with 89 per cent neutrophils. The nonprotein nitrogen was 135 mg., and the serum amylase was 108 units per 100 cc.; the lipase was 2.5 cc., and the sodium was 129.9 milliequiv., the potassium 3.1 milliequiv., and the chloride 98 milliequiv. per liter. On the next day the patient appeared sicker; the abdomen was distended, and there was tenderness in the right upper quadrant. The temperature was 101°F., and the pulse 145. The blood amylase was 51 units, and the nonprotein nitrogen 150 mg. per 100 cc. Two days later she had great difficulty in breathing, and although examination was difficult, one observer thought she might have collapse of or pneumonia of the lower lobe of the left lung. The urine had a specific gravity of 1.011 and gave a ++ test for albumin; the sediment contained 150 red cells per high-power field. Examination of the blood showed a hemoglobin of 10.7 gm. per 100 cc. and a white-cell count of 21,700, with 95 per cent neutrophils. The serum amylase was 61 units, the nonprotein nitrogen 160 mg., the calcium 11.9 mg., and the phosphorus 9.7 mg. per 100 cc., and the potassium was 2.6 milliequiv. per liter. On the following day the nonprotein nitrogen was 170 mg., and the total protein 5.7 gm. per 100 cc.; the carbon dioxide was 14.2 milliequiv., the chloride 88 milliequiv., the sodium 122.6 milliequiv., and the potassium 3.2 milliequiv. per liter; the pH was 7.4. During the next two days the patient deteriorated mentally and became incontinent of urine and feces. Rales were heard in the chest, multiple ecchymoses appeared, and a large, nodular slightly tender mass was palpable in the right upper quadrant extending across the abdomen. Peristalsis was absent; distention was marked. The patient was digitalized and seemed somewhat better, but the temperature, pulse rate and respirations began to rise further. On the following day the temperature was 103°F., the pulse 150, and the respirations 40. The white-cell count was 24,600. The serum nonprotein nitrogen was 170 mg., the calcium 9.0 mg., and the phosphorus 9.2 mg. per 100 cc. The abdominal mass had become larger and now extended down to the level of the umbilicus.

Early the next morning the patient died.

Differential Diagnosis

Dr. Marian W. Ropes*: This is a long history, but it seems to me that the first seven admissions and in essence the first three years of disease after the patient was first seen are relatively clear cut. When she was first seen she had evidence of generalized decalcification, presumably associated with the symptoms of aches and pains, that led to a pathologic fracture of the vertebra. Associated with this she had hypercalcemia, which I assume was in large part responsible for the symptoms of urinary frequency and constipation and probably for the personality changes; those symptoms did change after the first operation. The laboratory findings were corroborative of these two situations: the serum calcium was high; the phosphorus was not low, but in view of the kidney disease only slightly above the level of what one would expect; the alkaline phosphatase was very high; and the twenty-four-hour urine calcium excretion was above normal, 214 and 240 mg. per 100 cc. The x-ray films showed decalcification and a pathologic fracture. In addition the patient surely had renal disease, with abnormalities in the urine and a beginning retention of nonprotein nitrogen. When one seeks the cause of this combination of abnormalities, there are relatively few things to consider; everything in the picture is entirely consistent with hyperparathyroidism with associated kidney disease.

One would have to consider two other conditions in any patient with generalized bone disease and kidney disease. One is multiple myeloma; however there is nothing in the laboratory findings to support this diagnosis. The serum protein was normal; no abnormal cells were noted in the blood. The calcium, phosphatase and phosphorus findings would be very unusual; occasionally the calcium and phosphatase may be elevated, but they are rarely so high. The other condition one would have to consider is cancer metastasizing to bone. However, the generalized decalcification would not suit this; occasionally the serum calcium may be elevated but rarely to this height without treatment. There was nothing else to support it.

There was renal disease; one has to consider whether it was secondary to primary hyperparathyroidism, with renal calcinosis, or whether it was glomerulonephritis or pyelonephritis, with secondary hyperparathyroidism. The former is more likely, though at this stage I do not think there is any way to be sure of the type of renal disease. I believe the renal disease was not the primary cause of the hyperparathyroidism because the patient had too marked a degree of hyperparathyroidism for the degree of renal disease—they

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do not always correlate, but I think there is never such a degree of dissociation. One finding I do not understand is the high serum cholesterol. There was no evidence of hypothyroidism at this stage. The renal disease does not seem to have been the type that is associated with lipid elevation. I cannot rule out a familial or dietary hypercholesterolemia.

During the first admission, proof of the diagnosis was obtained by operation. The symptoms, signs and laboratory findings changed after the removal of the tumor.

Apparently, this tumor was a carcinoma of a parathyroid gland, with hyperparathyroidism, which is extremely rare. Dr. Castleman, when he reviewed all the parathyroid tumors in this hospital, found 3 cases of parathyroid carcinoma with hyperparathyroidism.* In the present case I have to accept the evidence of parathyroid carcinoma with hyperparathyroidism. During the next seven admissions there were recurrences of carcinoma, with fluctuations in symptoms and laboratory findings in accordance with recurrences of the nodules and removal of the tumors. Nothing during those admissions was inconsistent with the diagnosis already made. I think that the patient was at no time free from some hyperparathyroidism as judged by the laboratory findings; on occasions the findings approached normal, but not all of them were normal at the same time. During this period the renal failure apparently slowly increased.

During the last admission she had many new symptoms, chiefly gastrointestinal, and numbness in the legs. These symptoms were, I judge, thought to have been due to the hyperparathyroidism and the concurrent renal failure because she was operated on without any further search for other causes. There is no question that they could all have been due to this combination of diseases. A tumor was removed, apparently with some response of the hyperparathyroidism. This tumor was reported to be an adenoma. One surely has to raise the questions whether this was the recurrence of a carcinoma or whether secondary hyperparathyroidism had produced hyperplasia and the so-called adenoma. I find it difficult to know what the parathyroid tumor at this time was. My impression is that it was recurrent carcinoma. There was also a cyst in the fibula at this time. I think it would be well to see the x-ray films.

Dr. John F. Gibbons: When the patient originally came to the hospital there were apparently films from an outside hospital, and no films were taken here.

Dr. Oliver Cope: When the patient was first admitted, she was in so much pain from collapse of the vertebra that she could not be moved onto the x-ray table.

*Castleman, B. Tumors of parathyroid glands. Section IV, fascicle 15. 74 pp. In *Atlas of Tumor Pathology*. Washington, D. C.: Armed Forces Institute of Pathology, 1952.

Dr. Gibbons: The films on the second admission show generalized decalcification of the entire skeleton — of the spine, pelvis, skull and bony thorax. There is evidence of almost complete collapse of the body of the third lumbar vertebra and a slight degree of collapse of the third and fourth thoracic vertebras. She has diffuse punctate calcification in both kidneys (Fig. 1), and the ribs, like the rest of the skeleton, show demineralization. There are no localized cystic lesions in any of the bones at this time. In films made a year later a small localized lesion is seen for the first time; in the lower right fibula is an ovoid, expanding lesion typical of that seen in hyperparathyroidism. This does not suggest metastatic carcinoma, and there is no other localized lesion at that time. In a barium study done at this time there is no significant impression on the barium-filled esophagus to suggest recurrent tumor in that region. The rest of the films that I shall show were made at the time of the seventh admission, some three years after the original admission. At this time a barium study demonstrates a large impression on the right side of the barium-filled esophagus. If this represents an adenoma, it must certainly be a large one, and it is situated on the side opposite to the original tumor. This appearance could be due to the previous operation. The remaining films merely show changes that are about the same as those of the original films. The degree of decalcification in the kidneys is no greater, and the demineralization of the skeleton has not progressed. There is no further evidence of collapse of the vertebras although there may be slightly more kyphos deformity in the region of the third thoracic vertebra. The cystic lesion in the fibula has progressed and is now more expanding (Fig. 2). No new cystic lesion is found.

Dr. Ropes: The x-ray findings give corroboration of the fact that the hyperparathyroidism remained active throughout this period and was active at the time of the last admission as the symptoms, signs and result of operation suggest. I think there is no question that the lesion in the kidney was associated with the hyperparathyroidism. What else the patient had terminally is the question. All the symptoms and findings on admission could be associated with the hyperparathyroidism, hypercalcemia and renal disease. There is more evidence from the presence of renal calcinosis in the x-ray films, and I think without any question that the renal disease was secondary to the hyperparathyroidism, although she may also have had superimposed pyelonephritis.

What the mass slowly appearing in the abdomen was, and what caused the great rise in white-cell count and neutrophils, and the elevation in serum amylase, is a little hard to determine. I doubt that the pancreatic involvement that may have been present was associated either with metastases from the tumor or with another cancer, although those

two possibilities, like that of pancreatitis with some obstruction, cannot be absolutely ruled out. I think that she did have a terminal pneumonia and that she had severe progressive renal failure with a combination of all these contributing to her death.

In summary I shall say that this patient had a primary parathyroid carcinoma, with hyperparathyroidism active over many years, that she had renal disease initially secondary to the hyperparathyroidism and with some superimposed infection, and that she had a terminal pneumonia; to what degree the liver may have been involved and how much pancreatitis was present I cannot say.

Dr. Daniel S. Ellis: Dr. Ropes, you do not mean that you are not sure that she had pancreatitis? How are you going to explain the mass and the swollen abdomen and the high white-cell count?

Dr. Ropes: I think she had some pancreatitis, but whether that explains all the abdominal symptoms or not I do not know.

Dr. Ellis: I should think the terminal episode, the abdominal findings and the high amylase could certainly be explained by pancreatitis of some kind. Whether she had neoplasm, pseudocyst formation or pancreatitis secondary to gallstones, which she may have had, I cannot say. She certainly had involvement of the pancreas.

Dr. Jacob Lerman: The question of high cholesterol raises the possibility of hyperthyroidism. I wonder if the whole thyroid gland was removed when the first operation on the neck was done. There was a nodule on the right side when the left side was operated on; I wonder if the surgeon took out the rest of the lobe.

Dr. Ropes: The cholesterol was high before the operation.

Dr. Cope: There was no resection of thyroid tissue.

Dr. Philip Henneman: The mode of death in this case is somewhat suggestive of the picture that has been reported in patients with severe hyperparathyroidism complicated by advanced osteitis fibrosa generalisata. After the removal of the causative parathyroid tumor oliguria and uremia have developed, and the patients have died of renal failure. Unfortunately, the record does not give much information regarding the urinary output during the last two days of life.

Dr. Edward B. Benedict: The report sounds like metastatic carcinoma in the abdomen.

Dr. Benjamin Castleman: Before I call on Dr. Cope, I shall discuss the early part of this patient's disease. The original parathyroid carcinoma, which was one of the three that I reported previously, in part was encapsulated, but other parts were quite ragged owing to the fact that this tumor was adherent to the esophagus. That is the clue for the surgeon that he is dealing with a carcinoma rather than an adenoma. This photomicrograph of a section of the tumor shows an obvious carcinoma, with atypical cells merging with small round uniform cells characteristic of a parathyroid adenoma (Fig. 3). This is the first case that we have observed of a carcinoma possibly developing in an adenoma. The operation at which a right adenoma was removed was not as simple as stated in the abstract; the left side was explored very thoroughly, and

Figure 3.

nothing suggestive of recurrence was found; so on the chance that there might be something on the other side that had not been explored, Dr. Cope exposed the right side and removed a parathyroid adenoma — it was not secondary hyperplasia or carcinoma. I believe the finding of an adenoma on the opposite side is further evidence that the original tumor may also have been an adenoma before carcinoma developed in it.

Perhaps Dr. Cope will say something before I describe the autopsy.

Dr. Cope: Dr. Castleman has reviewed very well the sequence of events. At the first operation we initially thought that the tumor on the left side, a large tumor partly behind the esophagus and below

the lower pole of the thyroid gland, was probably a benign adenoma, but it was adherent and was difficult to remove. The recurrent nerve on the left ran in front of it and was adherent to it so I took special pains to spare the recurrent nerve. In trying to deliver the tumor from behind the recurrent nerve, in retracting on it and pushing it up from the bottom, I broke its capsule. We immediately recognized this and thought we had taken all the necessary precautions to prevent spread of cells, but obviously seeding occurred. The little nodule that could be felt at first and the five other nodules seen in the area of exposure must have been seeded. The removal of these at the second major operation only transiently altered the level of hyperparathyroidism. At the last operation, as Dr. Castleman explained, we found no residual tumor in the previous operative sites and went to the other side and found the benign adenoma. That is exciting because although there are 16 well documented cases of carcinoma in the literature, including 1 of our own previous cases, there is not a case in which there have been double tumors of which one was benign and the other malignant. Of course, we immediately think of the comparison with thyroid disease of multiple tumors, in which for many years it has been suspected that carcinoma may develop in a previously benign tumor.

One comment on the terminal illness: the patient was placed on chemotherapy because of the renal infection. For more than twenty days she received chloramphenicol until suddenly she began vomiting. Her physician immediately withdrew the antibiotic, but from that time on she was never well as far as the gastrointestinal tract was concerned. Dr. Ropes is quite right: the patient did die of a combination of diseases, but what relation the chloramphenicol therapy had to the death is a matter for speculation.

Clinical Diagnoses

Carcinoma of parathyroid gland, with metastases and hyperparathyroidism.
Chronic nephritis.
Acute pancreatitis.

Dr. Marian W. Ropes' Diagnoses

Parathyroid carcinoma, with hyperparathyroidism.
Renal disease secondary to hyperparathyroidism, with infection.
Pneumonia.
?Liver involvement.
Pancreatitis.

Anatomical Diagnoses

(Parathyroid carcinoma, left) with hyperparathyroidism and with metastases to liver.*
(Parathyroid adenoma, right.)
Acute pancreatitis, with fat necrosis of entire abdomen.
Renal calcinosis, with chronic pyelonephritis.
Calcinosis of lung and pancreas.
Osteitis fibrosa cystica.
Bronchopneumonia.

*Case No. 101 in the series of cases of hyperparathyroidism at the Massachusetts General Hospital.

Pathological Discussion

Dr. Castleman: At autopsy there were areas of fat necrosis scattered throughout the entire abdomen; the large mass that was felt was a piece of omentum diffusely involved with fat necrosis. The pancreas was about normal in size — slightly swollen but quite firm — and had scattered over its surface, and throughout, areas of fat necrosis, with numerous foci of calcification. The liver contained two small metastases — the only metastases in the body. There were none in the regional lymph nodes in the neck or mediastinum.

Dr. Cope: We thought that the patient must have had peripheral metastases somewhere, for the calcium level of the blood was not altered by the resection of the benign adenoma; therefore, she had to have actively secreting parathyroid tissue somewhere. The clinical difficulties of locating a metastasis are obvious when one looks at the size of the metastases — a walnut and a grape in the liver, one of which was deep in the right lobe of the liver. Surgically, though we might have reached the one extending to the posterior surface of the left lobe of the liver, we never could have found the one in the central portion of the right lobe.

Dr. Castleman: I think that of the 16 or 17 reported cases of parathyroid carcinoma there are 3 that had metastasized to the liver.

As was expected, there was extensive renal calcinosis. On microscopical examination there was very marked calcification throughout the interstitial tissue of the kidneys and a severe chronic pyelonephritis with obliteration of the tufts and tubules. Almost the entire right middle lobe of the lung was firm and yellowish white, and as we cut across it we knew we were cutting across deposits of calcium, which was quite sharply localized to specific areas. In other areas in the lung we did not feel this calcification when we sectioned it. A microscopical section of lung demonstrates how sharply divided the area of calcification is. The calcium appeared in the areas of pulmonary edema or of infection. Apparently, the calcification was localized to the areas of injury. Also, calcium had been deposited in the muscles traumatized during the operation.

The cystic lesion in the fibula was quite brown — the characteristic brown tumor that is often associated with hyperparathyroidism. Section showed osteitis fibrosa, with osteoblasts and osteoclasts. In most of the bones in this case the amount of change was slight, but in every section we could see some fibrosis along with bone trabeculae.

Microscopical examination of the pancreas demonstrated numerous foci of calcium. The most frequent locations for the calcinosis in hyperparathyroidism, both in man and in acute experimental parathyroid poisoning, are the kidney, the lung, the stomach and the heart. There have been two reports of calcification seen in the pancreas but the details are not too clear so that I cannot be sure how much calcification was present. There was a fair amount of calcification in the pancreas of this patient, and I should like to raise the point that the calcification may have been a factor in producing the pancreatitis. We found areas of fat necrosis with calcification around them, but we also found numerous areas of calcification without any fat necrosis. There was no evidence that the patient had pancreatitis before operation. I should like Dr. Albright's opinion about whether he thinks the calcification could have been the cause of the severe pancreatitis that developed postoperatively.

Dr. Fuller Albright: I think it could have been. You did not mention the thyroid gland when you listed the organs commonly involved in cases of metastatic calcification due to hyperparathyroidism.

Dr. Castleman: The thyroid gland did not show any calcification in this case, nor did we see any in the stomach.

Dr. Albright: When I worked with Professor Jacob Erdheim in Vienna, we killed several dogs with parathyroid-hormone overdosage. The organs involved in metastatic calcification were the three already mentioned: stomach, lungs and kidneys and, in addition, the thyroid gland.

Dr. Ropes: There was no explanation for the high cholesterol?

Dr. Castleman: No.

CASE 39102

Presentation of Case

A forty-six-year-old woman was transferred to this hospital in a semistuporous state.

The patient was apparently well and active until about a month before admission, when she noted pain in the left ear and left side of the head. She was seen by her physician, who found a temperature of 102°F., a questionable left otitis media and slight pharyngitis but no other positive findings. She was advised to remain in bed and was treated with penicillin and chloramphenicol. Symptoms and fever persisted, however, and the pain in the left ear and head became so severe that she required morphine for relief. Several days later she began to show signs of drowsiness, mental confusion, disorientation and restlessness and two days later she was admitted to another hospital. At this time the white-cell count was 18,000, with 70 per cent neutrophils and 30 per cent lymphocytes. A lumbar puncture was attempted, but no spinal fluid was obtained. She was then treated with aureomycin, 500 mg. every four hours, and streptomycin, 1 gm. twice a day. She continued to have mental symptoms, as well as generalized aches and pains, and began to show slight bilateral proptosis. The white-cell count at this time was 10,000. Another lumbar puncture yielded clear, xanthochromic spinal fluid under "low pressure," and jugular compression revealed a complete block. Examination of the spinal fluid disclosed 115 leukocytes per cubic millimeter, of which 70 per cent were neutrophils and 30 per cent lymphocytes. The protein was 112 mg. per 100 cc.; the sugar and chloride were not determined. Culture demonstrated no growth. She was transferred to another hospital for isolation. The white-cell count was 13,000; a lumbar puncture again yielded clear, xanthochromic spinal fluid with a differential white-cell count of 80 per cent lymphocytes and 20 per cent neutrophils (total count not given). Culture was again negative. During this time restlessness, confusion and disorientation had increased. The gait was described as very unsteady and the legs as stiff. On attempting to get out of bed the patient appeared to have no control of the legs; she was also noted to have "spasms" of both legs. She continued to run a febrile course. She gradually became semistuporous, and the legs became completely paralyzed and anesthetic.

For the two years before admission, the patient had complained of severe low-back pain, which was treated with massage and a heating pad.

Physical examination revealed a well developed, well nourished, semistuporous unco-operative woman. The pupils were equal; the right reacted more sluggishly to light than the left. There was slight papilledema bilaterally. There was an obvious flaccid paralysis of both lower extremities. An accurate sensory level could not be determined, but it was believed to be somewhere between the fourth and tenth dorsal dermatomes. Motor power and sensation seemed normal in the arms, and there was no other noticeable deficit above the fifth

thoracic dermatome; reflexes were absent below this level.

The temperature was 99°F., the pulse 80, and the respirations 20. The blood pressure was 130 systolic, 80 diastolic.

The urine had a specific gravity of 1.022 and gave a ++ test for albumin; the sediment contained 25 red cells, 12 white cells with occasional clumps, a few bacteria, frequent hyaline casts and a few granular casts per high-power field. Examination of the blood revealed a hemoglobin of 13.0 gm. and a white-cell count of 13,000, with 85 per cent mature and 1 per cent young neutrophils, 1 per cent late myelocytes, 11 per cent lymphocytes and 2 per cent monocytes.

Shortly after admission the patient was taken to the Radiology Department for myelography. However, a lumbar puncture could not be satisfactorily done, and only a few drops of xanthochromic spinal fluid were withdrawn; the fluid contained 250 red cells, 950 lymphocytes and 10 neutrophils per cubic millimeter and clotted easily. A short time later an operation was performed.

Differential Diagnosis

Dr. Robert S. Schwab*: I am dealing with the case of a forty-six-year-old woman with a two-year story of severe low-back pain and a one-month history of a progressive febrile illness involving a number of systems. In considering the groups of symptoms in this case, I shall start off with the highest cerebral centers and go downward. These highest centers were involved quite strikingly in a steadily progressive process evidenced first by drowsiness and confusion with irritability and then by a semicomatose state in which the patient was unco-operative for tests. Before the impairment of consciousness, she had severe headaches.

Another system involved was the circulation in the eyes, which was sufficiently interfered with so that there was bilateral papilledema on admission. The pupils appeared equal, but there was an asymmetry in their response to light; the significance of this is uncertain.

There were many symptoms referable to the spinal cord, beginning with the weakness of the legs and inability to control their movement, and ending in a complete paraplegia with loss of all sensation in the legs. The sensory level was indefinite; perhaps the correct sensory level to touch and pain was somewhere about the fifth, sixth and seventh thoracic dermatomes. Below this, all tendon reflexes had disappeared. The failure of the spinal-fluid pressure to rise on jugular compression is evidence of complete subarachnoid block. The spinal fluid itself contained a high total protein, the only value reported being 112 mg. per 100 cc., and was xanthochromic on three specimens — findings that fit in with the block. An inconsistent and puzzling laboratory finding was the cell count in this fluid. On one occasion the total cell count was 115 per cubic millimeter, with 70 per cent neutrophils and 30 per cent lymphocytes; this count was reversed after a change of hospital to 80 per cent lymphocytes and 20 per cent neutrophils, and that ratio was maintained up to the time of the attempted myelography, when the percentage was something like 95 per cent lymphocytes and about 5 per cent neutrophils, with a total of 960 cells per cubic millimeter — a large increase over the original count. This last fluid sample was reported to have clotted quite easily, and although no determination of the total protein was noted, I can assume that it was 200 or 300 mg. per 100 cc. at this point. All spinal-fluid specimens were sterile, and no sugar or chloride determinations were done. Conspicuous by its absence is a report of laboratory tests on both the blood and the spinal fluid.

In the urine there were casts and an increase of albumin (++ reaction). There are no reports of x-ray films and no mention of blood chemical determinations such as the total protein and albumin-globulin ratio.

To explain the involvement of all these different systems I have to choose either multiple pathologic processes, or one type of lesion in several places. I think it extremely unlikely for one lesion in one place to account for the many clinical findings. One always thinks of tumor of the spinal cord in association with spinal-fluid block and increased spinal-fluid protein, but such a process would not produce 960 cells per cubic millimeter in the fluid or the pronounced progressive mental deterioration with papilledema. I believe the same reservation can be made about an epidural abscess localized in the dorsal region; the high spinal-fluid cell count is somewhat against such an abscess, which would have to have spread downward for a considerable distance to involve the lumbosacral roots and thus to abolish all the reflexes in the legs as reported. I therefore think that abscess is unlikely.

*Neurologist, Massachusetts General Hospital.

A diffuse chronic inflammatory process can cause cerebral symptoms and cerebrospinal-fluid block, with increase in spinal-fluid cells and protein. One might think of gummas, but there is no convincing evidence of a syphilitic process. Moreover, there would have to be multiple gummas, which would be extremely unlikely. Chronically infected masses of granulomatous tissue scattered in the meninges near the fifth and sixth dorsal segments could produce the block; more of them further down could abolish the reflexes; and the same process in the intracranial cavity and in the meninges could cause the choking of the optic disks and the progressive mental deterioration. This seems to me a good possibility, but it would not explain the blood picture and the renal involvement.

This patient may have had lymphatic or myelogenous leukemia of the central nervous system. Actually, that is quite rare.* Leukemic tumor masses could very well compress the spinal cord, interfere with the peripheral nerves and, by deposits in the cranial cavity and around the vessels of the eyes, produce the papilledema, proptosis and mental changes. The cerebrospinal-fluid findings could fit that possibility, but the change from a preponderance of neutrophils to one of lymphocytes would be hard to explain unless one could assume that the normal cells were hard to identify in the ordinary low-power examination in the counting chamber. Leukemic cells often look like lymphocytes on low-power examination when they are actually myelocytes or young polymorphonuclear leukocytes, and some of the abnormal cells in lymphatic leukemia might be misidentified with polymorphonuclear leukocytes. The spinal-fluid cell count may be well over 100 in leukemia, but I cannot remember that it has ever been as high as 960. The high total protein could result from leukemic infiltration of the subarachnoid space, so that this finding would also be consistent. On the other hand, the blood picture, with a white-cell count that started at 18,000 and dropped slowly to 10,000, would be hard to explain even though the differential count showed the young forms. Lymphatic leukemia is a tempting diagnosis to make. Leukemic infiltration of the kidney would explain the urinary findings. All the findings would then seem to be tightly sewn together.

*Schwab, R. S., and Weiss, S. Neurologic aspects of leukemia. *Am. J. M. Sc.* **189**:766-777, 1935.

Multiple myeloma with invasion of the spinal canal is another possibility. There is a hint of that from the albumin in the urine, but it is not specified that this was Bence-Jones protein. The blood protein was not given. Multiple myeloma can block the spinal canal but would not produce a high cell count in the spinal fluid.

If I am to pick a diagnosis, I shall choose a chronic infective process with granulomas involving the spinal cord, the meninges of the spinal cord below the cord lesion, the meninges behind the eye causing the papilledema, and the meninges over the cerebral hemispheres causing the mental deterioration. My second choice is a chronic leukemia involving the same areas.

Clinical Diagnosis

?Epidural abscess.

Dr. Robert S. Schwab's Diagnosis

Chronic infective process, with granulomas involving meninges of spinal cord and brain.

Anatomical Diagnoses

Tuberculous meningitis.
Tuberculous endometritis, caseous.
Miliary tuberculosis.

Pathological Discussion

Dr. Winfield S. Morgan: Dr. Javid, you operated on this patient; will you describe your findings?

Dr. Manucher Javid: This patient was seen by a neurosurgeon in another hospital, who sent her to us for an exploratory laminectomy to rule out an epidural abscess. She was so confused and stuporous that she could not give us any history. Attempted myelography was unsuccessful. On the basis of the sensory findings we did a thoracic laminectomy of the seventh, eighth and part of the ninth thoracic vertebras. No epidural abscess was found. The dura had no granulations and was not thickened; however, it was adherent to the arachnoid. The arachnoid contained white material, which obscured the spinal cord. The cord was pale and felt soft. We passed a catheter upward and downward in the subarachnoid space; it went upward for 4 or 5 cm. and downward for 6 or 7 cm. It was our impression that this patient had a meningomyelitis, and we made smears for acid-fast bacilli and took cultures.

After operation the course was downhill, and she died on the third postoperative day.

DR. MORGAN: I shall ask Dr. Richardson to discuss the neuropathological findings.

DR. EDWARD P. RICHARDSON, JR.: The most striking finding on removal of the brain and spinal cord was generalized thickening of the leptomeninges, with dense whitish subarachnoid exudate most abundant over the base of the brain and over the cord. In the subarachnoid space along the large fissures of the convex surfaces of the cerebral hemispheres, there were numerous tiny, round clumps of whitish exudate, characteristic of small tubercles. On section of the brain, similar tiny, whitish elevations studded the ependymal walls of the ventricles. At the operative site, in the midthoracic region of the spinal cord, the dura and leptomeninges were markedly adherent, and the cord in this region was softened. Microscopical examination showed extensive inflammatory disease of the meninges, characterized by a cellular exudate made up chiefly of lymphocytes and large mononuclear cells, with foci of necrosis of exudate, and with epithelioid and giant-cell formation. In the midthoracic portion of the spinal cord, there was recent necrosis of cord tissue, most marked at the periphery, with relative sparing of the gray and white matter centrally. In association with this, there was necrosis and occasional thrombosis of small meningeal vessels entering the cord. The findings were entirely consistent with diffuse tuberculous meningitis and meningomyelitis, with sealing off of the foramens of the fourth ventricle by exudate at the base of the brain.

DR. CHARLES S. KUBIK: I should not hesitate to make an out-and-out diagnosis of tuberculous meningitis. Considering the character of the subarachnoid exudate and tubercles, I do not believe it could have been anything else, even though tubercle bacilli were not demonstrated.

DR. WALTER BAUER: Could coccidiomycosis do this?

DR. KUBIK: I have not seen it with anything else.

DR. RAYMOND D. ADAMS: Was the thoracic part of the spinal cord necrotic?

DR. RICHARDSON: There was acute necrosis of the thoracic part of the spinal cord, without evidence of any chronic destructive changes.

DR. ADAMS: Did that have the appearance of infarct necrosis, or was it merely an inflammation of the spinal-cord substance?

DR. RICHARDSON: It was the picture of very recent infarct necrosis.

DR. ADAMS: The development of paraplegia is unusual. I have seen this only rarely in tuberculous meningitis. This type of spinal-cord lesion is sometimes classed as tuberculous myelitis. The process, however, is one of infarction of the cord from vascular occlusion and should be distinguished from Pott's paraplegia, which is a compressive myelopathy.

DR. MORGAN: The gross examination of the other organs, except for the uterus, did not tell us very much. There were a few pleural adhesions bilaterally, but the lungs were light and not remarkable. The endometrial cavity was filled with soft, yellowish material that on microscopical examination proved to be caseous tuberculosis. There were miliary tubercles in the lung, liver and spleen, lymph nodes and kidneys. One hesitates to suggest that this was primary tuberculosis of the uterus since almost all cases of tuberculosis in the uterus are secondary to a primary lesion in the lungs; however, in view of the advanced stage of development of the lesions in the uterus in comparison to those found in other organs, it seems fair to suggest that the miliary dissemination had its source in the uterus.

Evaluation of Clinicopathological Exercises. To evaluate the place of the clinicopathological conference in medical education, Dr. Castleman would like to obtain a list of the groups that use the Case Records of the Massachusetts General Hospital as a teaching exercise in their society or hospital meetings, dinner clubs, student conferences and so forth. If it becomes practical, would your group be interested in obtaining pertinent lantern slides of roentgenograms, specimens and so forth with each case? Replies indicating the method used in the group should be made directly to Dr. Castleman, Massachusetts General Hospital, Boston 14. Comments and suggestions will be welcome.

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THE DOCTOR TAKES HIS PEN IN HAND

Doctors, certainly as much as the members of any profession, appear to have found it spiritually profitable to turn their talents, at times, into other fields. Many physicians and surgeons have hobbies — in some cases quite unexpected ones, and in others avocations that fall in line with the manual dexterity required in their daily work. Not a few surgeons in the old days made many of their own instruments and carved their bone handles; they have been cabinetmakers, builders of violins, sculptors and artists and tiers of dry flies. Some of these doctors who have achieved unusual prominence in their side line, or made it their main line, are now being given recognition as "Doctors Afield," in the *Journal's* department of Medical Intelligence.

It is to literature, however, that physicians seem most naturally to turn; perhaps it is the way with the members of all vocations, who are able to hold a pencil, for the itch that leads one into scratching with this implement is widely distributed. Doctors who write may be somewhat arbitrarily and yet with some logic divided into three groups.

The first, whose members are counted by the hundreds, consists of those who, with greater or less training in medicine, have yet forsaken it, or practically forsaken it, to produce their literary masterpieces. Among the greatest of these is that physician now known as St. Luke, who dedicated himself finally to the writing of a Gospel, and whose name is forever associated with it. Nicholas Copernicus, trained as a physician, left the medical profession to found a new science and establish its validity with one of the great books of all time. A few names picked almost at random may serve as other examples of this group — Rabelais, Goldsmith, Keats, Schiller, Arthur Conan Doyle, Cronin — with no belittlement intended of the hundreds of others whose names are of necessity omitted.

The second group, numbered in the thousands, consists of those physicians who, still holding to some form of professional employment, have found pleasure or profit in nonprofessional writing. Such are Sir Thomas Browne, Oliver Wendell Holmes, Sir William Osler, Weir Mitchell and Albert Schweitzer.

The third group includes every doctor who ever toiled over a paper for his hospital bulletin or district-society journal, as well as nearly all those in the second group, many of whom have made great contributions to the literature of their profession.

Six writings in particular are bold milestones in the course of medical literature. The *Hippocratic Collection*, whether actually written by the Father of Medicine or transcribed by his disciples, constitutes the essence of his teachings and of his love of the art, which sprang from his love of man.

Nineteen centuries later the twenty-eight-year-old Vesalius brought medicine out of its long passage through the Dark Ages with his brilliant *De humanis corporis fabrica*, published in 1543 almost con-

comitantly with Copernicus's book about the stars. Forty years later Ambroise Paré, certainly the parent of surgery if surgery ever had one, published the famous *Journeys in Diverse Places*, in which he dressed the wound for God's healing.

Three great books, though small, make up the second half of this group of asteroids. In 1628 William Harvey's treatise *On the Movement of the Heart and Blood* appeared, and in 1685 William Withering's *An Account of the Foxglove*, which elicited the following anonymous lines:

The foxglove leaves, with caution given,
Another proof of favoring Heaven
Will happily display.
The rapid pulse it can abate,
The Hectic flush can moderate
And, blest by Him Whose will is fate,
May give a lengthened day.

The third of these and the last of the six great works was published over a hundred and fifty years ago, although only eighteen years after Withering's little volume had made its appearance. Entitled *An Inquiry into the Causes and Effects of the Variolae Vaccinae*, seventy-five pages in length, it concerned the contribution to medicine of Edward Jenner, "a country practitioner who was destined to save more lives than the wars which raged during his lifetime had destroyed."

Immortals are being born today, too, but they lack the opportunity of standing out above the crowd that was vouchsafed those of a less populous and a less competitive era.

TO THE ABSENT MEMBERS

Inexorable fate, operating through an ancient ruling of the Massachusetts Medical Society, has decreed that those fellows of the Society who have not by March 1 of any year discharged their current indebtedness to the organization shall be deprived of that weekly benefit to which they look forward with such eagerness — the receipt of the *Journal*. For their annual levy, which is, incidentally, the only levy on which the treasurer has to work, is due and payable on January 1, and two moons are allowed to wax and wane before the penalty is exacted and the ax allowed to fall.

The *Journal*, more than willing to soften any blow with which its family of subscribers is threatened, has made it an immemorial custom to delay the final severance of relations until well into the month, even without promise of payment. Notwithstanding this friendly consideration, however, 785 of the First Physicians of Massachusetts were deprived of their *Journal* for varying periods of time in 1949; 651 paid the penalty in 1950; 1370 were cut from the list in 1951 and 1053 suffered a like fate in 1952.

Prompt correction of the fiscal error restores the legendary privilege of receiving the publication, but, alas, without the missing numbers. These, not having been printed for the delinquent members, can never be restored.

APPRAISAL OF THE ADOLESCENT

A neglected field of medicine has been that of adolescence; the explanation is simple. Until recently, the pediatrician has been preoccupied with premature babies, transfusions, feeding problems, running ears and such routine but weighty considerations as vitamin deficiencies and the acute communicable diseases. The adolescent has survived most of these, and the mother has lived long enough with her child to learn that a frantic telephone call to the doctor is no longer necessary for a 1° rise in temperature or for the appearance of a new tooth — even a wisdom tooth. The internist has also been busy with the ills of adulthood and advancing age and has still to come to the period of adolescence. Yet the field is particularly important, marking as it does the transition from boy to man and from girl to woman.

Adolescence not only presents its own specific challenges, which emerge in importance as nutritional disorders and infections are brought under control, but also is a valuable period for checking the results of past illnesses and therapy and the assay of present constitution with which the child is equipped, well or ill, to meet the stresses of the future. Perhaps the foundation of hypertension, heart disease, peptic ulcer, arthritis and the like is already being laid.

Chief matters to be kept in mind in dealing with the adolescent are the patient's concern with his own growth and development and with school problems and the urge toward strenuous living —

emotional as well as physical. Size and state of maturity are matters of much greater moment to members of this age group than they are to younger or older people. Going to school is a chief occupation for the young, and failure to do well may cause a variety of symptoms manifested by physical complaints as well as unacceptable behavior. Finally, youth lives strenuously, and this fact has to be kept in mind when one is planning daily routines and treatment of and convalescence from disease. In dealing with persons who are neither children nor adults one needs to know a good deal about the many conditions that can result in failure of physical or scholastic progress, and to possess a considerable knowledge of their sports and extracurricular emotional concerns. Changing attitudes toward religion, divorce, death and the behavior of parents, heroes and other adults may confuse them; they need success, recognition, independence and a healthy understanding of sex.

Because of these considerations and because there is a crying need for the scientific evaluation of the adolescent (especially of objective data about his psychologic status) as the product of the past and the potential problem of the future, the establishment of an adolescent unit at the Boston Children's Hospital is of more than passing interest in the second half of the twentieth century.

If, as has been indicated, chief concern is with the medical, endocrine and psychologic problems presented by these large children or small adults — depending on how they are viewed — the challenge is no less clear that it is time to stop theorizing about many of their ailments and to begin to collect objective evidence about the psyche and its interactions with the soma that may lead to better treatment, with the hope of prevention in a dimly seen future.

After an examination of the Journals of Dentistry for the past year, we are constrained, as an act of justice to the fraternity, to say, that the amount of original matter they have contained, and most of it of sterling value, shows that the dental profession of the United States have not been surpassed in their literary efforts by any body of professionals among us.

Boston M. & S. J., *March 9, 1853*

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

RICHARDSON — Wyman Richardson, M.D., of Newton, died on February 1. He was in his fifty-seventh year.

Dr. Richardson received his degree from Harvard Medical School in 1923. He was formerly associate in medicine at Harvard Medical School and a member of the staff and of the general executive committee of the Massachusetts General Hospital, and was a fellow of the American College of Physicians and American Medical Association.

He is survived by his widow, two sons and two daughters.

PETER — Alphonse J. Peter, M.D., of Newburyport, died on February 5. He was in his sixty-sixth year.

Dr. Peter received his degree from Tufts College Medical School in 1911. He was formerly a member of the staff of Anna Jaques Hospital.

He is survived by his widow.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

GAMMA GLOBULIN FOR MEASLES

Attention is called to the fact that the recommended dose of gamma globulin for the modification of measles is now 0.01 cc. per pound of body weight. Since the need for such modification is primarily in children, the total amount needed will seldom exceed 1 cc. This would be enough to modify the disease in a child weighing 100 pounds.

For this reason the amount of gamma globulin furnished by the Department for measles will hereafter be only 1 cc. per vial.

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR JANUARY, 1953

RÉSUMÉ

DISEASE	JANUARY 1953	JANUARY 1952	SEVEN-YEAR MEDIAN
Chancroid	3	4	3
Chicken pox	4945	1865	2322
Diphtheria	1	4	15
Dog bite	611	644	611
Dysentery, bacillary	13	0	4
Encephalitis, infectious	2	8	2
German measles	165	783	98
Gonorrhea	241	182	238
Granuloma inguinale	0	0	0
Hepatitis, infectious	108	10	3†
Lymphogranuloma venereum	0	2	1
Malaria	1	0	1
Measles	158	9565	1167
Meningitis, meningococcal	11	8	7
Meningitis, Pfeiffer bacillus	6	6	4
Meningitis, pneumococcal	1	4	4
Meningitis, staphylococcal	0	0	0
Meningitis, streptococcal	0	0	0
Meningitis, undetermined	7	7	5
Mumps	1098	1890	1517
Poliomyelitis	7	2	1
Salmonellosis	13	3	4
Scarlet fever	549*	349	651
Syphilis	89	292	212
Trichinosis	1	1	3
Tuberculosis, pulmonary	184	174	207
Tuberculosis, other forms	6	16	12
Typhoid fever	0	0	0
Undulant fever	1	1	2
Whooping cough	136	373	454

*Includes streptococcal sore throat.

†Four-year median.

Comment

Diseases below the seven-year median were diphtheria, measles, mumps, scarlet fever and whooping cough.

Only 1 case of diphtheria was reported in January, bringing the total cases for the seven months since July 1, 1952, to only 3.

The 158 and 136 reported cases of measles and whooping cough, respectively, made these the lowest figures for the month of January in the history of Massachusetts.

Diseases above the seven-year median included chicken pox, bacillary dysentery, German measles, meningococcal meningitis, poliomyelitis and salmonellosis.

The 4945 cases of chicken pox reported represented the highest figure ever reported in this state for the month of January.

The 13 cases of salmonellosis reported constituted the highest figure for the month of January ever recorded.

Infectious hepatitis (jaundice) is being recognized from widely separated areas. This disease has been occurring all along. Word is just getting around that it should be reported, so the numbers reported might give an erroneous idea that it is greatly on the increase. It has increased in a few communities.

Geographical Distribution of Certain Diseases

The following diseases were reported from the communities named:

Diphtheria: Brookline, 1.

Dysentery, bacillary: Boston, 1; Cambridge, 1; Chelsea, 1; Grafton, 1; Holyoke, 1; Hull, 1; Revere, 1; Wrentham, 6; total, 13.

Encephalitis, infectious: Easthampton, 1; Sutton, 1; total, 2.

Hepatitis, infectious: Beverly, 1; Boston, 10; Cambridge, 2; Camp Edwards, 1; Cohasset, 4; Fall River, 1; Fort Devens, 2; Greenfield, 1; Haverhill, 1; Hanson, 1; Holden, 2; Leicester, 1; Millbury, 12; Needham, 1; Newton, 1; Pittsfield, 1; Shrewsbury, 1; Springfield, 1; Waltham, 1; Weston, 1; Worcester, 47; Wrentham, 15; total, 108.

Malaria: Fort Devens, 1.

Meningitis, meningococcal: Amherst, 1; Boston, 1; Cambridge, 1; Cohasset, 1; Falmouth, 2; North Adams, 1; Revere, 1; Southboro, 1; Stockbridge, 1; Waltham, 1; total, 11.

Meningitis, mumps: Framingham, 1.

Meningitis, Pfeiffer bacillus: Beverly, 2; Lawrence, 1; New Bedford, 2; Weymouth, 1; total, 6.

Meningitis, pneumococcal: Lawrence, 1.

Meningitis, undetermined: Brockton, 1; Cambridge, 1; Chicopee, 1; Everett, 1; Grafton, 1; Quincy, 1; Somerville, 1; Wellesley, 1; total, 8.

Poliomyelitis: Boston, 1; Cambridge, 2; East Longmeadow, 1; Revere, 1; Springfield, 1; Worcester, 1; total, 7.

Salmonellosis: Boston, 1; Everett, 1; Gardner, 1; Malden, 1; Medford, 1; Newton, 4; Revere, 2; Tewksbury, 1; Wellesley, 1; total, 13.

Trichinosis: Lynn, 1.

Undulant fever: Saugus, 1.

CORRESPONDENCE

RESTORATION OF LICENSE

To the Editor: This is to inform you that the registration of Dr. David Ginsburg, 175 State Street, Springfield, has been restored to him by order of the Suffolk Supreme Court as of February 5, 1953.

Robert C. Cochrane, M.D.
Secretary
Board of Registration in Medicine

State House
Boston

REGARDING TRANSPERITONEAL DIALYSIS

To the Editor: In the excellent paper by Drs. Marcel Legrain and John P. Merrill entitled "Short-Term Continuous Transperitoneal Dialysis," which appeared in the January 22 issue of the *Journal*, reference is made to the risk of peritoneal infection and the measures taken to prevent it. It was the high incidence of peritonitis in our patients, who were continuously irrigated for forty-eight hours or more, that led us to abandon the method. We were particularly disinclined to exploit the method after further studies, which demonstrated that the infection, usually due to *Escherichia coli*, was not caused by contamination of the irrigating fluid or any other error in technic, but by transmural migration of intraintestinal bacteria. Experimental data indicated that the irritating properties of the fluid, combined with the uremic state, facilitate the process of peritoneal invasion. Moreover, the Kolff apparatus, as modified by the investigators at the Peter Bent Brigham Hospital, was obviously superior in many respects. The recommendation by Drs. Legrain and Merrill of the short-term period of irrigation for certain cases of acute renal failure is, I believe, warranted on the basis of their evidence. But I also believe that the danger of infection from intraintestinal organisms is not wholly obviated by reliance solely upon the antibiotics that they use in the irrigating fluid. Control of the intraintestinal bacteria should be better assured by the use of an effective antibiotic, such as neomycin or aureomycin, given orally before and during irrigation therapy.

Jacob Fine, M.D.

Boston

BOOK REVIEW

A Guide to the History of Science: A first guide for the study of the history of science, with introductory essays on science and tradition. By George Sarton, Sc.D., L.H.D., LL.D., editor of *Isis* and *Osiris*, and formerly professor of the history of science, Harvard University. Waltham, Massachusetts: Chronica Botanica Company, 1952. $7.50.

Dr. Sarton, in this new book, has provided an invaluable tool for the historian of science in all its branches. The work is divided into two parts. The first and shorter part, intended to explain the purpose and meaning of the history of science, reproduces three lectures first delivered in 1948 at the University of London. The lectures, intended for serious reading, discuss science and tradition, ancient and medieval science and the possibility of teaching the history of science. The second part of 235 pages comprises a series of bibliographies of reference tools, divided into four sections as follows: history and science in general, the history of science and the organization, study and teaching of the subject; the history of science in special countries, in cultural groups, in special sciences (including anatomy and physiology, medicine and dentistry), and journals and serials; and lists of institutes, museums and libraries, and international congresses.

In passing, it should be noted that the Boston Medical Library has a collection illustrating the history of medicine, especially in Massachusetts, in addition to the Storer collection of approximately 4000 medals, coins, tokens and badges of medical interest. The guide is a fundamental reference tool and is recommended for all medical and other libraries and to all persons interested in the history of medicine and science.

James F. Ballard

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Antibiotics: Being the fifty-second Robert Boyle Lecture delivered before the Oxford University Scientific Club on June 1st, 1951. By Professor Sir Howard Florey, F.R.S., M.A., Ph.D., Sir William Dunn School of Pathology, Oxford. 8°, cloth, 35 pp., with 22 illustrations. Oxford, England: Blackwell Scientific Publications, 1951. (Distributed by Charles C Thomas, Springfield, Illinois, $1.50.)

In this lecture Professor Florey discusses the biology, production and application to treatment of the various antibiotics.

Personality: Symposia on topical issues. Edited by Werner Wolff. Vol. I, numbers 3 and 4. November 1951. 8°, paper, 388 pp. New York: Grune and Stratton, 1951. $2.00.

These numbers of a new periodical contain a number of articles on hypnosis and personality and hypnotherapy.

Klinische Physiologie und Pathologie. By Professor Dr. Ferdinand Hoff, director, I. medizinischen Universitätsklinik, Frankfurt-am-Main. Second, revised edition. 8°, cloth, 810 pp., with 133 illustrations. Stuttgart: Georg Thieme, 1952. Ganzleinen 49.50. (Distributed by Grune and Stratton, New York.)

The first edition of this comprehensive treatise was published in 1950 and went out of print within a year. The author has revised the text and added some illustrations to the second edition. The material is arranged by systems: circulatory, respiratory, the blood and blood-forming organs, liver, gall bladder and pancreas, the intestinal canal, the kidney and urinary tract, locomotor system, the vegetative nervous system, internal secretions, metabolism and allergy. The last chapter is devoted to a short history of the subject. The extensive pertinent literature is surveyed throughout the text. There is a bibliography arranged by chapters, and indexes of authors and subjects. The text is written in simple, easily understandable German. The publishing is excellent, and the book is recommended for all collections on clinical physiology and pathology.

Bacitracin: A review and digest of the literature up to and including January, 1952. 8°, cloth, 127 pp., with 11 illustrations and 30 tables. New York: Research Division, S. B. Penick and Company, 1952. $4.00.

This monograph presents a survey of the literature of the antibiotic from its discovery in 1945 to the present time. There is a bibliography of 198 titles.

Clinical Pathology Data. Compiled by C. J. Dickinson, B. A., B. Sc., University College Hospital Medical School, London. With a foreword by C. E. Dent, Ph.D., M.D., M.R.C.P., F.R.I.C., reader in medicine in the University of London. 8°, paper, 32 pp. Oxford, England: Blackwell Scientific Publications, 1951. (Distributed by Charles C Thomas, Springfield, Illinois, $0.64.)

This small pamphlet provides in simple tabular form pathological data on blood, cerebrospinal fluid, feces, gastric contents, plasma and serum, urine and glucose tolerance curves (GTC). The last table presents 19 well known special tests. There is a section of practical notes on tests that can be performed without elaborate laboratory equipment. There is an index to diseases with reference to the various tests.

Hautplastiken: Indikation und Technik. By Privatdozent Dr. Med. H. U. Buff, chief physician, Chirurgischen Universitäts-Klinik, Zürich. With an introduction by Professor Dr. Med. A. Brunner, Zürich. 8°, cloth, 136 pp., with 173 illustrations. Stuttgart: Georg Thieme, 1952. Ganzl. DM 22.50. (Distributed by Grune and Stratton, New York.)

This monograph on skin transplantation discusses the various types and methods of operation. It is a practical book, well illustrated, and should be in all collections on the subject.

Neurosurgery: An historical sketch. By Gilbert Horrax, M.D., Sc.D., chief, Neurosurgical Service, The Lahey Clinic, and neurosurgeon, New England Baptist Hospital and New England Deaconess Hospital, Boston. 8°, cloth, 135 pp., with 41 illustrations. Springfield, Illinois: Charles C Thomas, 1952. $3.75. (Publication No. 117, *American Lecture Series.*)

The author of this monograph discusses the history of neurosurgery in seven sections, which may be divided roughly into two sections, ancient and modern. The ancient period, from prehistoric and Egyptian times to 1700 A.D., includes the Greek, medieval and renaissance epochs. The modern period, beginning with 1700, discusses the pre-Listerian and pre-Horsley periods, and the era of neurosurgery as a surgical specialty, 1890 to date. Approximately half the text is devoted to this last period. Dr. Horrax has endeavored to point out the highlights of each period and to summarize the advances made in neurosurgery from one period to another. There is a bibliography of 181 titles. The book is well illustrated. The lack of an index detracts from its reference value. It should be in all collections on medical history and neurology.

Physiological Changes in Plasma Proteins Characteristic of Human Reproduction: Cross-sectional and Longitudinal Electrophoretic Data for Women During and Following Uncomplicated and Complicated Pregnancies. By Icie G. Macy, Ph.D., Sc.D., director of the Research Laboratory, Children's Fund of Michigan, Detroit; and Harold C. Mack, M.D., Department of Obstetrics and Gynecology, Harper Hospital, Detroit. 8°, paper, 170 pp., with 14 illustrations and 11 tables. Detroit, Michigan: Childrens' Fund of Michigan [1952].

This special monograph is devoted to a study of plasma proteins and blood plasma proteins, before, during and after pregnancy as revealed by electrophoresis.

NOTICES

SOCIETY MEETINGS AND CONFERENCES

MARCH 6. Massachusetts Society of Anesthesiologists. Page 395, issue of February 26.

MARCH 6–27. Combined Anesthesia Teaching Conferences of Boston. Page 210, issue of January 29.

MARCH 6–30. Springfield Hospital Educational Program. Page 396, issue of February 26.

MARCH 7. Antibiotics: Specific Indications. Drs. Maxwell Finland and Louis Weinstein. Mount Auburn Hospital, Cambridge. 10:05 a.m.

MARCH 8–10. Alumni Postgraduate Convention. College of Medical Evangelists. Page 266. issue of February 5.

MARCH 9 AND 23. Postgraduate Course in General Medicine. Cushing Veterans Administration Hospital, Framingham. Page 697, issue of October 30.

MARCH 9–27. Consultation Clinics for Crippled Children in Massachusetts. Page 353, issue of February 19.

MARCH 9–MAY 4. Massachusetts Department of Mental Health. Postgraduate Seminar in Neurology and Psychiatry. Page 540, issue of October 2.

MARCH 10. Harvard University Career Conference in the Medical Sciences. Page 395, issue of February 26.

MARCH 10. Harvard Medical Society. Page 353, issue of February 19.

MARCH 11. New England Pediatric Society. Page 395, issue of February 26.

MARCH 11 AND APRIL 1. Postgraduate Medical Institute Course in General Medicine. Burbank Hospital, Fitchburg. Page 1049, issue of December 25.

MARCH 11–APRIL 8. Postgraduate Medical Institute. Boston. Page 452, issue of September 18.

MARCH 12. Pentucket Association of Physicians. Pentucket Club, Haverhill. 8:30 p.m.

MARCH 13. Gardner Postgraduate Seminar. Henry Heywood Memorial Hospital, Gardner. 6:00–8:00 p.m.

MARCH 13. New England Center Hospital House Officers' Association. Page 395, issue of February 26.

MARCH 16–APRIL 20. Hartford Medical Society. Page 42, issue of January 1.

MARCH 17. Boston Evening Clinic. Page 395, issue of February 26.

MARCH 17. South End Medical Club. Page 307, issue of February 12.

MARCH 25. Cutter Lecture. Page 307, issue of February 12.

MARCH 25. Graduate Club of Boston, Phi Delta Epsilon Medical Fraternity. Page 307, issue of February 12.

APRIL 10. New England Society of Anesthesiologists. Page 395, issue of February 26.

APRIL 10–12. American Association of the History of Medicine. Page 308, issue of February 12.

APRIL 15. Massachusetts Academy of General Practice. Spring Clinical Assembly. Hotel Shelton, Boston.

APRIL 16–18. Boston Lying-in Hospital Postgraduate Course in Obstetrics and Pediatrics. Page 307, issue of February 12.

APRIL 19–24. National Industrial Health Conference. Page 308, issue of February 12.

APRIL 25. Alumni Association of the State University College of Medicine at New York City. Page 396, issue of February 26.

APRIL 25. Graduate Club of Boston, Phi Delta Epsilon Medical Fraternity. Page 307, issue of February 12.

APRIL 29 AND OCTOBER 28. New England Obstetrical and Gynecological Society. Page 868, issue of November 27.

MAY 19–21. Massachusetts Medical Society. Hotel Statler, Boston.

MAY 25–31. First World Congress on Fertility and Sterility. Page 1001, issue of December 18.

JUNE 7–9. American College of Cardiology. Page 395, issue of February 26.

DISTRICT MEDICAL SOCIETIES

ESSEX NORTH

MAY 13. Andover Country Club, Shawsheen.

MIDDLESEX SOUTH

MARCH 7. Margaret Jewett Hall, Mount Auburn Hospital. 10:05 a.m.

(*Notices concluded on page xv*)

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1. Hechter, O.; Dopkeen, S. K., and Yudell, M. H.: The Clinical Use of Hyaluronidase in Hypodermoclysis, J. Pediat. 30:645 (June) 1947.
2. Schwartzman, J.; Henderson, A. T., and King, W. E.: Hyaluronidase in Fluid Administration: A Preliminary Report, J. Pediat. 33:267 (Sept.) 1948.

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(*Additional advertisements on page xv*)

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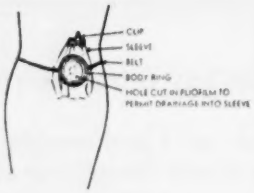

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NOTICES (*Concluded from page 440*)

MIDDLESEX WEST

MARCH 9 AND 23. Postgraduate Course in General Medicine. Cushing Veterans Administration Hospital, Framingham.

NORFOLK

MARCH 24.

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, MARCH 12

THURSDAY, MARCH 12

*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.

9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.

11:00 a.m.–12:00 m. Pediatric Conference, Mount Auburn Hospital, Cambridge.

*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.

5:00 p.m. Case Presentation and Pathological Discussion followed by a Subject of Special Presentation. Joslin Amphitheater, New England Deaconess Hospital.

*5:00–6:00 p.m. Surgical Division Meeting. Mount Auburn Hospital, Cambridge.

FRIDAY, MARCH 13

*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.

*10:00 a.m.–1:00 p.m. Medical and Surgical Grand Rounds. Dr. George W. Thorn and Dr. Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.

10:30–11:15 a.m. Diabetes Lecture. Dr. Elliott Joslin. New England Deaconess Hospital.

12:00 m.–1:00 p.m. Clinicopathological Conference (Boston Floating Hospital). Joseph H. Pratt Diagnostic Hospital.

*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.

*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.

*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Waltham Street.

*7:00 p.m. New England Center Hospital House Officers' Association. Stearns Auditorium, New England Center Hospital.

*7:00–9:00 p.m. Combined Anesthesia Teaching Conference of Boston. Amphitheater, Evans Memorial, Massachusetts Memorial Hospitals, Eighth Floor, 65 East Newton Street.

SATURDAY, MARCH 14

*9:00 a.m. Proctology Clinic. Peter Bent Brigham Hospital.

*9:00 a.m. Alcoholism Clinic. Peter Bent Brigham Hospital.

*11:00 a.m.–12:00 m. Blood Clinic. Dr. William Dameshek. Stearns Auditorium, New England Center Hospital.

MONDAY, MARCH 16

*8:00–9:00 a.m. Combined Medical and Surgical Rounds for Diabetic Surgery Cases. New England Deaconess Hospital.

*8:30–9:30 a.m. Clinic by entire Surgical Staff and Anesthesia Staff. Cheever Amphitheater, Dowling Building, Boston City Hospital.

12:00 m. Pediatric Medical-Surgical Conference (Boston Floating Hospital). Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.

*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.

*2:00–8:30 p.m. Postgraduate Seminar in Neurology and Psychiatry. Metropolitan State Hospital, Waltham.

*7:00–9:00 p.m. Anesthesia Teaching Conference. Stearns Auditorium, New England Center Hospital.

TUESDAY, MARCH 17

*9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.

11:00 a.m.–12:00 m. Regular Grand Rounds of the Pediatric Department. Dowling Amphitheater, Boston City Hospital.

*12:00 m.–1:00 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.

*12:15–1:15 p.m. X-ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.

5:00 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.

*5:00–6:00 p.m. Service Meeting followed by Clinical Conference (Medical, Surgical, Obstetrical). Faulkner Hospital.

*8:00 p.m. Boston Evening Clinic. Clinic Building.

WEDNESDAY, MARCH 18

*12:00 m. Boston State Hospital Psychiatric Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.

*12:00 m.–1:00 p.m. Clinicopathological Conference. (Children's Medical Center.) Jimmy Fund Building, 25 Binney Street.

12:30 p.m. Weekly Pathological Meeting. Joslin Amphitheater, New England Deaconess Hospital.

*4:00 p.m. Thoracic Conference. Held by Overholt Clinic. Harris Hall, New England Deaconess Hospital.

*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.

*7:30 p.m. Lahey Clinic Lecture. Chest Diseases. Drs. Carlton R. Souders, David P. Boyd, Herbert D. Adams and Stewart H. Jones. Joslin Auditorium, New England Deaconess Hospital.

*Open to the medical profession.

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Index to Advertisers

	PAGE
The Chester A. Baker Laboratories, Inc.	xv
Baldpate, Inc.	xiv
Boston Diagnostic Clinic	xiv
Ciba Pharmaceutical Products, Inc.	Back Cover
David Memorial Nursing Home	xiv
Electroencephalographic Laboratory, Inc.	xii
Glenside, Inc.	xiv
Hanover House, Inc.	xiv
Hollister-Stier Laboratories	ix
Kenmore Clinical Laboratory, Inc.	xii
Leary Laboratory	xii
Lederle Laboratories	After viii
Eli Lilly and Company	x
C. Frederick MacGill Associates	xii
E. F. Mahady Co.	xiv
Merck & Company, Inc.	vii
Parke, Davis and Company	ii, iii
The E. L. Patch Co.	vi
Perkins School	xiv
Charles Pfizer & Co., Inc.	v
Philip Morris & Co., Ltd.	xiii
Ring Sanatorium	xiv
W. B. Saunders Company	Front Cover
G. D. Searle and Company	xi
Southern Medical Supply Co.	viii
Storrow House (Massachusetts General Hospital)	xii
United States Brewers Foundation, Inc.	viii
Washingtonian Hospital	xv
Wiswall Sanatorium	xiv
Woodside Cottages, Inc.	xiv
Wyeth, Inc.	iv

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